

FORM PTO-1390 (Modified)
(REV 11-2000)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER

TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 U.S.C. 371

206704US0PCT

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR

09/830559

INTERNATIONAL APPLICATION NO.
PCT/JP99/06166INTERNATIONAL FILING DATE
05 NOVEMBER 1999PRIORITY DATE CLAIMED
05 NOVEMBER 1998 (earliest)

TITLE OF INVENTION

NOVEL COMPOUNDS AND PHARMACEUTICAL USE THEREOF

APPLICANT(S) FOR DO/EO/US

Hisaaki CHAKI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
 - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
 - b. ☒ has been communicated by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☒ is attached hereto.
 - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
 - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
 - b. ☐ have been communicated by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Request for Consideration of Documents in International Search Report
Notice of Priority / PCT/IB/304 / PCT/IB/308

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 09/830559)		INTERNATIONAL APPLICATION NO. PCT/JP99/06166	ATTORNEY'S DOCKET NUMBER 206704US0PCT																																															
24. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) : <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO \$1000.00 <input checked="" type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO \$860.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO \$710.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) \$690.00 <input type="checkbox"/> International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) \$100.00 ENTER APPROPRIATE BASIC FEE AMOUNT = Surcharge of \$130.00 for furnishing the oath or declaration later than _____ months from the earliest claimed priority date (37 CFR 1.492 (e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30			CALCULATIONS PTO USE ONLY <table border="1" style="width:100%; border-collapse: collapse;"><tr><td>\$860.00</td><td></td></tr><tr><td>\$0.00</td><td></td></tr></table>	\$860.00		\$0.00																																												
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a. <input checked="" type="checkbox"/> A check in the amount of <u>\$3,086.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>15-0030</u> . A duplicate copy of this sheet is enclosed. d. <input type="checkbox"/> Fees are to be charged to a credit card. WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.																																																		
NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.																																																		
SEND ALL CORRESPONDENCE TO:																																																		
22850		SIGNATURE <u>Norman F. Oblon</u> NAME <u>24,618</u> REGISTRATION NUMBER <u>MAY 7 2001</u> DATE																																																
(703) 413-3000		Surinder Sachar Registration No. 34,423																																																

Docket No.: 206704US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
Hisaaki CHAKI, et al. : ATTN: APPLICATION DIVISION
SERIAL NO.: 09/830,559 :
FILED: MAY 7, 2001 :
FOR: NOVEL COMPOUNDS AND MEDICINAL USE THEREOF

PRELIMINARY AMENDMENT AND STATEMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

In response to the Office communication mailed November 20, 2001, please
amend the above-identified application as follows:

IN THE SPECIFICATION

Please amend the specification as shown in the attached marked-up copy to
read as follows:

Please replace the formula on page 6, between prenumbered lines 8 and 9,
as follows:

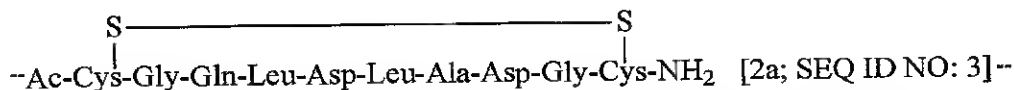
--Ac-Cys¹-Gly²-AA³-AA⁴-AA⁵-AA⁶-AA⁷-AA⁸-Gly⁹-Cys¹⁰-NH₂ [2; SEQ ID NO:1]-

-

Please replace the formula on page 6, between prenumbered lines 18 and
19, as follows:

--Ac-aa⁰-Cys¹-Gly²-aa³-aa⁴-aa⁵-aa⁶-aa⁷-Gly⁸-aa⁹-Cys¹⁰-NH₂ [2b, SEQ ID NO:2]--

Please replace the formula on page 21, between prenumbered lines 1 and 2,
as follows:



Please replace the paragraph at page 21, prenumbered lines 4-15, as
follows:

--Subsequently, a three-dimensional structure of a complex compound of peptide [2a; SEQ ID NO:3] and a partial structure containing the DNA binding site of AP-1 were prepared by the use of SYBYL, and a molecular dynamics simulation was carried out according to the molecular dynamics calculation program AMBER (Oxford Molecular Co., GB) (Fundamentals of Protein Engineering Physics and Chemistry, published by Kyoritsu Shuppan, Page 192, 1991) by using the three-dimensional structure obtained above as an initial structure to obtain a plurality of three-dimensional structures of AP-1-cyclic peptide [2a; SEQ ID NO:3] complex in water.--

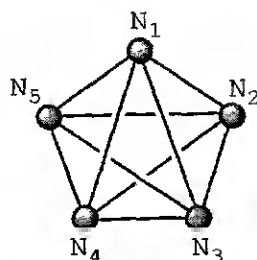
Please replace the paragraph at page 21, prenumbered lines 16-23, as
follows:

--On the other hand, nuclear magnetic resonance (NMR) spectrum of peptide [2a; SEQ ID NO:3] was measured, and the result was treated according to a structural analysis software X-PLOR (MSI Co., USA) to obtain a plurality of three-dimensional structures of peptide [2a; SEQ ID NO:3] in water experimentally (Shinsei Kagaku Jikken Koza I, Proteins III, Pages 139-147, 1990, published by

Tokyo Kagaku Dojin).--

Please replace the paragraph at page 21, prenumbered line 24, to page 22, prenumbered line 21, as follows:

--The experimentally obtained three-dimensional structures were compared with the three-dimensional structures of cyclic peptide [2a; SEQ ID NO:3] in the complex obtained from the molecular dynamics simulation. As a result, a high level of similarity was found out between eleven of the experimentally confirmed three-dimensional structures and fourteen of the three-dimensional structures obtained from molecular dynamics simulation in the partial three-dimensional structure of Gln-Leu-Asp-Leu-Ala [SEQ ID NO:4]. Based on this finding, it could be confirmed that the five atoms N_1 , N_2 , N_3 , N_4 and N_5 expressed by the following formula:



wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group, constitute a pharmacophore necessary for the binding to AP-1 and the expression of an antagonistic activity to AP-1 binding sequence (Souyaku Kagaku, Kagaku Dojin,

Pages 11-13, 1995).--

Please replace the list at page 52, prenumbered line 12, to page 53, prenumbered line 28, as follows:

--As typical compounds of this invention, the following compounds can be referred to, for example, provided that Ac represents an acetyl group.

- Ac-Cys-Gly-Gln-Leu-Asp-Lcu-Ala-Leu-Gly-Cys-NH₂ [SEQ ID NO:5] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Leu-Gly-Cys-NH₂ [SEQ ID NO:6] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Gly-Gly-Cys-NH₂ [SEQ ID NO:7] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Asn-Gly-Cys-NH₂ [SEQ ID NO:8] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Asp-Gly-Cys-NH₂ [SEQ ID NO:9] (having a disulfide linkage between the first and tenth cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Asp-Leu-Ala-Asp-Gly-Cys-NH₂ [SEQ ID NO:3] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Asn-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:10] (having a disulfide linkage between the second and eleventh L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Lcu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:11] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Asn-Cys-Gly-Asn-Ala-Leu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:12] (having a disulfide linkage between the second and eleventh L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Asp-Cys-NH₂ [SEQ ID NO:13] (having

- Please replace the paragraph at page 96, prenumbered lines 7-22, as follows:

Please replace the paragraph at page 99, prenumbered lines 20-25, as follows:

Please replace the paragraph at page 100, prenumbered lines 16-19, as follows:

--The peptide of general formula [8; SEQ ID NO:1] can be obtained by removing the protecting group of amino side chain and the resin from the protected peptide resin of general formula [7; SEQ ID NO:1] in the presence of an acid.--

Please replace the paragraph at page 101, prenumbered lines 21-26, as follows:

--The cyclic peptide of general formula [2; SEQ ID NO:1] can be obtained by forming a disulfide linkage between the cysteine side chains of the peptide of general formula [8; SEQ ID NO:1]. The formation of intramolecular disulfide linkage between two cysteine residues can be effected according to a known method.--

Please replace the paragraph at page 102, prenumbered lines 12-23, as follows:

--The cyclic peptides of general formula [2; SEQ ID NO:1] or salts thereof thus obtained can be isolated and purified according to conventional methods such as extraction, crystallization, gel filtration, liquid chromatography and/or column chromatography. For example, the isolation and purification can be effected by the gel filtration method using a gel filter such as Sephadex G-10, G-25 or the like, the column chromatography using a reverse phase type synthetic polymer resin or a chemically modified silica gel carrier and/or a high performance liquid chromatography, or the like.--

Please replace the paragraph at page 102, prenumbered lines 25-27, as follows:

--The cyclic peptide of general formula [2b; SEQ ID NO:2] can be obtained by the same method as Production Process 1.--

Substitute page 384 (Abstract), after the last line, beginning at a new page,
please insert the attached sequence listing.

IN THE CLAIMS

Please amend the claims as shown in the attached marked-up copy to read
as follows:

--5. (Amended) A peptide of 10 residues represented by the following
amino acid sequence:

Ac-Cys¹-Gly²-AA³-AA⁴-AA⁵-AA⁶-AA⁷-AA⁸-Gly⁹-Cys¹⁰-NH₂ [SEQ ID NO:1]

wherein Ac represents an acetyl group, AA³ represents a polar amino acid residue,
each of AA⁴, AA⁶ and AA⁷ represents a hydrophobic amino acid residue, AA⁵
represents an amino acid residue having carboxyl or hydroxyl group in the side
chain thereof, and AA⁸ represents an arbitrary amino acid residue; said peptide
having a disulfide linkage between the first and tenth cysteine residues; or a salt
thereof.--

--7. (Amended) A peptide of 10 or 11 residues represented by the
following amino acid sequence:

Ac-aa⁰-Cys¹-Gly²-aa³-aa⁴-aa⁵-aa⁶-aa⁷-Gly⁸-aa⁹-Cys¹⁰-NH₂ [SEQ ID NO:2]

wherein Ac represents an acetyl group, aa⁰ represents an arbitrary amino acid
residue or a bonding unit, aa³ represents a polar amino acid residue, each of aa⁴, aa⁵
and aa⁷ represents a hydrophobic amino acid residue, aa⁶ represents an arbitrary
amino acid residue, and aa⁹ represents an amino acid residue having carboxyl or
hydroxyl group in the side chain thereof; provided that, when aa⁰ is a bonding unit,
said peptide has a disulfide linkage between the first and tenth cysteine residues

and, when aa⁰ is an arbitrary amino acid residue, said peptide has a disulfide linkage between the second and eleventh cysteine residues; or a salt thereof.--

BASIS FOR THE AMENDMENT

Claims 5 and 7 have been amended.

All of the present amendments are supported by the specification as originally filed. The amendments have been made to insert sequence identifiers, which correspond to the attached sequence listing. No new matter is believed to have been added by these amendments.

REMARKS

Claims 1-40 are pending in the present application.

Applicants have now submitted a Sequence Listing and a corresponding computer readable Sequence Listing. The sequence information recorded in the corresponding computer readable Sequence Listing is identical to the paper copy of the Sequence Listing. Support for all the sequences listed in the Sequence Listing are found in the present application as originally filed. No new matter is believed to have been introduced by the submission of the Sequence Listing and the corresponding computer readable Sequence Listing.

Applicants submit that the present application is ready for examination on the merits. Early notice to this effect is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24, 618

Daniel J. Pereira, Ph.D.
Registration No. 45,518

Tel: (703) 413-3000
Fax: (703) 413-2220
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Marked-Up Copy

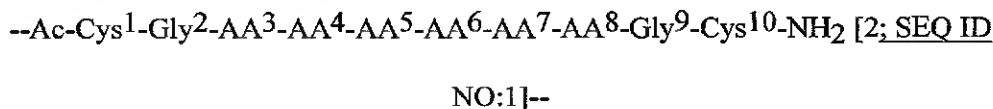
Docket No.: **206704US0 PCT**

Serial No: **09/830,559**

IN THE SPECIFICATION

Please amend the specification as follows:

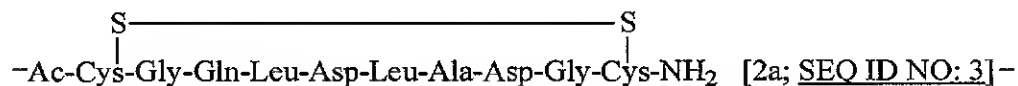
Please replace the formula on page 6, between prenumbered lines 8 and 9,
as follows:



Please replace the formula on page 6, between prenumbered lines 18 and
19, as follows:



Please replace the formula on page 21, between prenumbered lines 1 and 2,
as follows:



Please replace the paragraph at page 21, prenumbered lines 4-15, as
follows:

--Subsequently, a three-dimensional structure of a complex compound of
peptide [2a; SEQ ID NO:3] and a partial structure containing the DNA binding site
of AP-1 were prepared by the use of SYBYL, and a molecular dynamics simulation
was carried out according to the molecular dynamics calculation program AMBER

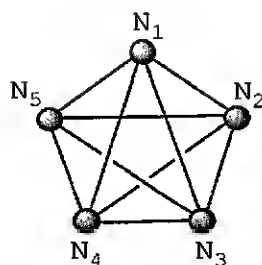
(Oxford Molecular Co., GB) (Fundamentals of Protein Engineering Physics and Chemistry, published by Kyoritsu Shuppan, Page 192, 1991) by using the three-dimensional structure obtained above as an initial structure to obtain a plurality of three-dimensional structures of AP-1-cyclic peptide [2a; SEQ ID NO:3] complex in water.--

Please replace the paragraph at page 21, prenumbered lines 16-23, as follows:

--On the other hand, nuclear magnetic resonance (NMR) spectrum of peptide [2a; SEQ ID NO:3] was measured, and the result was treated according to a structural analysis software X-PLOR (MSI Co., USA) to obtain a plurality of three-dimensional structures of peptide [2a; SEQ ID NO:3] in water experimentally (Shinsei Kagaku Jikken Koza I, Proteins III, Pages 139-147, 1990, published by Tokyo Kagaku Dojin).--

Please replace the paragraph at page 21, prenumbered line 24, to page 22, prenumbered line 21, as follows:

--The experimentally obtained three-dimensional structures were compared with the three-dimensional structures of cyclic peptide [2a; SEQ ID NO:3] in the complex obtained from the molecular dynamics simulation. As a result, a high level of similarity was found out between eleven of the experimentally confirmed three-dimensional structures and fourteen of the three-dimensional structures obtained from molecular dynamics simulation in the partial three-dimensional structure of Gln-Leu-Asp-Leu-Ala [SEQ ID NO: 4]. Based on this finding, it could be confirmed that the five atoms N₁, N₂, N₃, N₄ and N₅ expressed by the following formula:



wherein N₁ represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N₃ represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N₂, N₄ and N₅ independently represent an arbitrary carbon atom constituting a hydrophobic group, constitute a pharmacophore necessary for the binding to AP-1 and the expression of an antagonistic activity to AP-1 binding sequence (Souyaku Kagaku, Kagaku Dojin, Pages 11-13, 1995).--

Please replace the list at page 52, prenumbered line 12, to page 53, prenumbered line 28, as follows:

- As typical compounds of this invention, the following compounds can be referred to, for example, provided that Ac represents an acetyl group.
- Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Leu-Gly-Cys-NH₂ [SEQ ID NO:5] (having a disulfide linkage between the first and tenth L-cysteine residues)
 - Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Leu-Gly-Cys-NH₂ [SEQ ID NO:6] (having a disulfide linkage between the first and tenth L-cysteine residues)
 - Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Gly-Gly-Cys-NH₂ [SEQ ID NO:7] (having a disulfide linkage between the first and tenth L-cysteine residucs)
 - Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Asn-Gly-Cys-NH₂ [SEQ ID NO:8] (having

a disulfide linkage between the first and tenth L-cysteine residues)

- Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Asp-Gly-Cys-NH₂ [SEQ ID NO:9] (having a disulfide linkage between the first and tenth cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Asp-Leu-Ala-Asp-Gly-Cys-NH₂ [SEQ ID NO:3] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Asn-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:10] (having a disulfide linkage between the second and eleventh L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:11] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Asn-Cys-Gly-Asn-Ala-Leu-Ala-Leu-Gly-Ser-Cys-NH₂ [SEQ ID NO:12] (having a disulfide linkage between the second and eleventh L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Asp-Cys-NH₂ [SEQ ID NO:13] (having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ser-Leu-Gly-Asp-Cys-NH₂ [SEQ ID NO:14] (having a disulfide linkage between the first and tenth L-cysteine residues)--

Please replace the paragraph at page 96, prenumbered lines 7-22, as follows:

--The peptide-bonded resin of general formula [7; SEQ ID NO:1] can be obtained by subjecting the resin of general formula [6] to a solid phase method. The construction of peptide chain by solid phase method is carried out by repeating a condensation of amino acid having an amino acid functional group protected with appropriate protecting group and de-protection of the protecting group of α -amino acid. Condensation of amino acid is carried out successively one by one from the terminal amino acid according to the order of amino acids in the sequence to be

synthesized. The procedure of the solid phase method will be mentioned below. A series of reactions used therein are preferably carried out in an atmosphere of nitrogen. Any of the manual method and the method of using an automatic synthesizing apparatus may be adopted.--

Please replace the paragraph at page 99, prenumbered lines 20-25, as follows:

--(4) The peptide of general formula (7; SEQ ID NO:1) can be obtained by acetylating a peptide-bonded resin having 10 residues. Concretely, it can be obtained by reacting a peptide-bonded resin of 10 residues with acetic anhydride in the presence or absence of an amine.--

Please replace the paragraph at page 100, prenumbered lines 16-19, as follows:

--The peptide of general formula [8; SEQ ID NO:1] can be obtained by removing the protecting group of amino side chain and the resin from the protected peptide resin of general formula [7; SEQ ID NO:1] in the presence of an acid.--

Please replace the paragraph at page 101, prenumbered lines 21-26, as follows:

--The cyclic peptide of general formula [2; SEQ ID NO:1] can be obtained by forming a disulfide linkage between the cysteine side chains of the peptide of general formula [8; SEQ ID NO:1]. The formation of intramolecular disulfide linkage between two cysteine residues can be effected according to a known method.--

Please replace the paragraph at page 102, prenumbered lines 12-23, as follows:

--The cyclic peptides of general formula [2; SEQ ID NO:1] or salts thereof thus obtained can be isolated and purified according to conventional methods such as extraction, crystallization, gel filtration, liquid chromatography and/or column chromatography. For example, the isolation and purification can be effected by the gel filtration method using a gel filter such as Sephadex G-10, G-25 or the like, the column chromatography using a reverse phase type synthetic polymer resin or a chemically modified silica gel carrier and/or a high performance liquid chromatography, or the like.--

Please replace the paragraph at page 102, prenumbered lines 25-27, as follows:

--The cyclic peptide of general formula [2b; SEQ ID NO:2] can be obtained by the same method as Production Process 1.--

Substitute page 384 (Abstract), after the last line, beginning at a new page, please insert the attached sequence listing.

IN THE CLAIMS

Please amend the claims as follows:

--5. (Amended) A peptide of 10 residues represented by the following amino acid sequence:

Ac-Cys¹-Gly²-AA³-AA⁴-AA⁵-AA⁶-AA⁷-AA⁸-Gly⁹-Cys¹⁰-NH₂ [SEQ ID NO:1]

wherein Ac represents an acetyl group, AA³ represents a polar amino acid residue, each of AA⁴, AA⁶ and AA⁷ represents a hydrophobic amino acid residue, AA⁵ represents an amino acid residue having carboxyl or hydroxyl group in the side chain thereof, and AA⁸ represents an arbitrary amino acid residue; said peptide

having a disulfide linkage between the first and tenth cysteine residues; or a salt thereof.--

--7. (Amended) A peptide of 10 or 11 residues represented by the following amino acid sequence:

Ac-aa⁰-Cys¹-Gly²-aa³-aa⁴-aa⁵-aa⁶-aa⁷-Gly⁸-aa⁹-Cys¹⁰-NH₂ [SEQ ID NO:2]

wherein Ac represents an acetyl group, aa⁰ represents an arbitrary amino acid residue or a bonding unit, aa³ represents a polar amino acid residue, each of aa⁴, aa⁵ and aa⁷ represents a hydrophobic amino acid residue, aa⁶ represents an arbitrary amino acid residue, and aa⁹ represents an amino acid residue having carboxyl or hydroxyl group in the side chain thereof; provided that, when aa⁰ is a bonding unit, said peptide has a disulfide linkage between the first and tenth cysteine residues and, when aa⁰ is an arbitrary amino acid residue, said peptide has a disulfide linkage between the second and eleventh cysteine residues; or a salt thereof.--

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22850

Docket No. 206704US0PCT

JC17 Rec'd PCT/PTO 16 JUL 2001

IN RE APPLICATION OF: Hisaaki CHAKI, et al.

SERIAL NO: 09/830,559

FILED: May 7, 2001

FOR: NOVEL COMPOUNDS AND PHARMACEUTICAL USE THEREOF

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

TECH CENTER 1600/2900

SEP 17 2001

RECEIVED



Transmitted herewith is an amendment in the above-identified application.

No additional fee is required

Small entity status of this application under 37 C.F.R. §1.9 and §1.27 is claimed.

Additional documents filed herewith: Marked-Up Copy; Abstract

The Fee has been calculated as shown below:

CLAIMS	CLAIMS REMAINING		HIGHEST NUMBER PREVIOUSLY PAID	NO. EXTRA CLAIMS	RATE	CALCULATIONS	
TOTAL	40	MINUS	82	0	× \$18 =	\$0.00	
INDEPENDENT	13	MINUS	13	0	× \$80 =	\$0.00	
		<input type="checkbox"/> MULTIPLE DEPENDENT CLAIMS			+ \$270 =	\$0.00	
		TOTAL OF ABOVE CALCULATIONS					\$0.00
		<input type="checkbox"/> Reduction by 50% for filing by Small Entity					\$0.00
		<input type="checkbox"/> Recordation of Assignment				+ \$40 =	\$0.00
		TOTAL					\$0.00

A check in the amount of _____ is attached.

Please charge any additional Fees for the papers being filed herewith and for which no check is enclosed herewith, or credit any overpayment to deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. §1.136, and any additional fees required under 37 C.F.R. §1.136 for any necessary extension of time may be charged to Deposit Account No. 15-0030. A duplicate copy of this sheet is enclosed.

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No. 24,618

Richard L. Treanor, Ph.D.
Registration No. 36,379



22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 10/00)

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SERIAL NO: 09/830,559

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☒ Small entity status of this application under 37 C.F.R. §1.9 and §1.27 is claimed.

☒ Additional documents filed herewith: Marked-Up Copy; Abstract

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INDEPENDENT	13	MINUS	13	0	× \$80 =	\$0.00	
		<input type="checkbox"/> MULTIPLE DEPENDENT CLAIMS			+ \$270 =	\$0.00	
		TOTAL OF ABOVE CALCULATIONS					\$0.00
		<input type="checkbox"/> Reduction by 50% for filing by Small Entity					\$0.00
		<input type="checkbox"/> Recordation of Assignment				+ \$40 =	\$0.00
		TOTAL					\$0.00

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MAIER & NEUSTADT, P.C.

Norman F. Oblon
Registration No. 24,618

Richard L. Treanor, Ph.D.
Registration No. 36,379



22850

Tel. (703) 413-3000
Fax. (703) 413-2220
(OSMMN 10/00)



206704US0PC

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :
CHAKI HISAAKI ET AL : ATTN: APPLICATION DIVISION
SERIAL NO: 09/830,559 :
FILED: MAY 7, 2001 :
FOR: NOVEL COMPOUNDS AND :
PHARMACEUTICAL USE :
THEREOF :

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

SIR:

Prior to examination on the merits, please amend the above-identified application as follows.

IN THE ABSTRACT

Please replace the Abstract with the new Abstract attached as a separate sheet.

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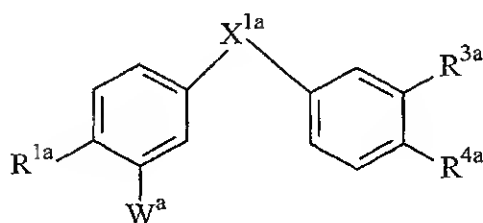
IN THE CLAIMS

Please amend the claims as shown on the marked-up copy following this amendment to read as follows.

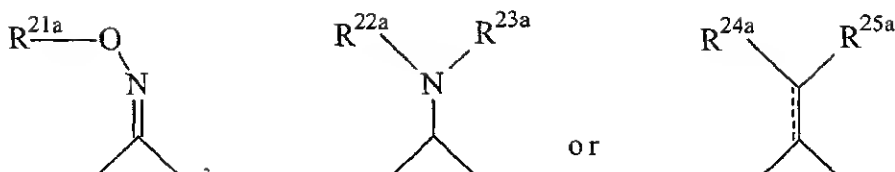
3. (Amended) A compound or a salt thereof according to Claim 1, wherein N₁ constituting the pharmacophore is a nitrogen atom of unsubstituted or substituted amino, ammonium, amido, thioamido, ureido, isoureido, amidino, guanidino, thioureido, hydrazino or hydrazono group to which one or more hydrogen atoms are bonded, a carbon atom of ethenyl group to which a hydrogen atom is bonded, an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfonyl group, an oxygen atom of sulfonyloxy group, an oxygen atom of sulfo group, an oxygen atom of sulfinyl group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, a sulfur atom of mercapto group, an oxygen atom of hydroxyl group, an oxygen atom of ester or a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group; N₃ is an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfo group, an oxygen atom of sulfonyl group, an oxygen atom of sulfo group, an oxygen atom of sulfonyloxy group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, an oxygen atom of hydroxyl group, an oxygen atom of ester, a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group to which no hydrogen atom is combined, a nitrogen atom of sulfonamido group or a nitrogen atom of acylsulfonamido group; and each of N₂, N₄ and N₅ is an arbitrary carbon atom constituting a carbon atom of alkyl group, a carbon atom of alkenyl group, a carbon atom of aryl group and a carbon atom of alkoxy group.

4. (Amended) A compound or a salt thereof according to Claim 1, wherein a compound having an atom corresponding to N₃ and atoms corresponding to two or more atoms selected from N₁, N₂, N₄ and N₅ among the atoms N₁, N₂, N₃, N₄ and N₅ constituting a pharmacophore, and, in the optimized three-dimensional structure thereof, the interatomic distances between the atom corresponding to N₃ and the two or more atoms selected from N₁, N₂, N₄ and N₅ are the atomic distances of a pharmacophore has an activity of antagonistically inhibiting the binding between AP-1 (activator protein-1) and a recognition sequence thereof.

16. (Amended) A benzene derivative represented by the following formula:



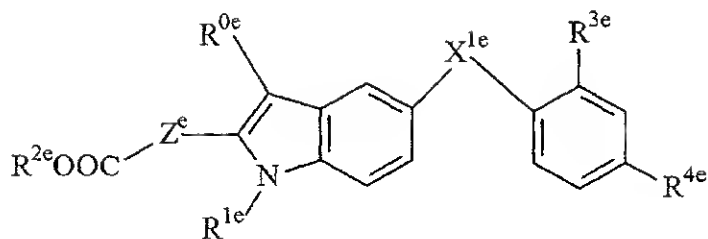
wherein R^{1a} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{3a} and R^{4a} may be the same or different represent a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1a} represents -C(O)-, -CH(OH)-, -CH₂- or a group of the following formula:



wherein R^{21a} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group; R^{22a} and R^{23a} may be the same or different represent a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, carbamoyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^{24a} and R^{25a} may be the same or different represent a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; and the double line of which one line is a broken line represents a single bond or a double bond and W^a represents $-Z^a-COR^{26a}$, $-Z^a-COOR^{2a}$, $-O-CH_2COOR^{2a}$ or $-O-CH_2CH_2COOR^{2a}$ (wherein Z^a represents $-(CH_2)_n-$ (n is 1, 2 or 3), $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; R^{2a} represents a hydrogen atom or a protecting group for carboxyl group; and R^{26a} represents $-NHR^{27a}$ or $-NHSO_2R^{28a}$ (R^{27a} and R^{28a} independently represent an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group));

or a salt thereof.

24. (Amended) A benzene derivative represented by the following general formula:

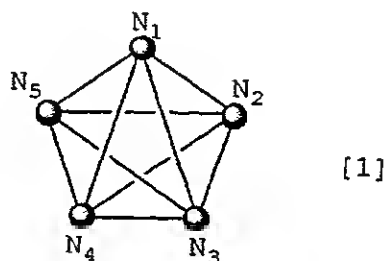


wherein R^{0e} represents a hydrogen atom, a halogen atom, a nitro group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxy carbonyl, alkylsulfonylamino or arylsulfonylamino group; R^{1e} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxy carbonyl or alkylsulfonyl group; R^{2e} represents a hydrogen atom or a protecting group for carboxyl group; R^{3e} and R^{4e} may be the same or different represent a hydrogen atom, a halogen atom, an unprotected or protected hydroxyl group, a unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group, provided that both R^{3e} and R^{4e} cannot simultaneously be a hydrogen atom; X^{1e} represents -C(O)-, -CH(OH)- or -CH₂-; and Z^e represents -(CH₂)_n- (n^e represents 0, 1 or 2) or -CH=CH-;

or a salt thereof.

29. (Amended) A compound or a salt thereof according to Claim 9, wherein said compound is a compound that has an activity of antagonistically inhibiting the combination between AP-1 and a recognition sequence thereof.

30. (Amended) A compound comprising the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 , said atoms constitute the pharmacophore represented by the following formula 1:



wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_4 and N_5 is not less than 4 angstroms and not

more than 9 angstroms; and, in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; and a salt thereof, wherein the compound conforming to a pharmacophore is a peptide or a benzene derivative according to Claim 9.

31. (Amended) A method for inhibiting AP-1 which comprises administering a compound or a salt thereof according to Claim 1.

32. (Amended) An agent for preventing and treating a disease into which an excessive expression of AP-1 participates, which comprises a compound or a salt thereof according to Claim 1.

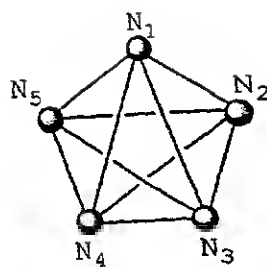
33. (Amended) An agent for preventing and treating an autoimmune disease, which comprises a compound or a salt thereof according to Claim 1.

34. (Amended) An AP-1 inhibitor comprising a compound or a salt thereof according to Claim 1.

Please add new Claims 35-40 as follows:

35. (New) A compound or a salt thereof according to Claim 9, wherein said compound is a compound that has an activity of antagonistically inhibiting the combination between AP-1 and a recognition sequence thereof.

36. (New) A compound comprising the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 , said atoms constitute the pharmacophore represented by the following formula 1:



[11]

wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_4 and N_5 is not less than 4 angstroms and not more than 9 angstroms; and, in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; and a salt thereof, wherein the compound conforming to a pharmacophore is a peptide or a benzene derivative according to Claim 9.

37. (New) A method for inhibiting AP-1 which comprises administering a compound or a salt thereof according to Claim 9.

38. (New) An agent for preventing and treating a disease into which an excessive expression of AP-1 participates, which comprises a compound or a salt thereof according to Claim 9.

39. (New) An agent for preventing and treating an autoimmune disease, which comprises a compound or a salt thereof according to Claim 9.

40. (New) An AP-1 inhibitor comprising a compound or a salt thereof according to Claim 9.

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REMARKS

The Abstract in the original application has been replaced with a new Abstract. The new Abstract contains less than 150 words.

Claims 1-40 are active in the present application. Claims 3-4 and 29-34 have been amended to remove multiple dependencies. Support for new Claims 35-40 is found in the original Claims 1-34. Claims 16 and 24 have been corrected for clarity. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Norman F. Oblon
Attorney of Record
Registration No. 24,618

Richard L. Treanor, Ph.D.
Registration No. 36,379



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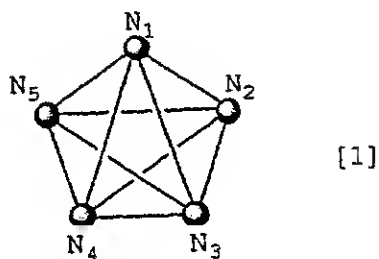
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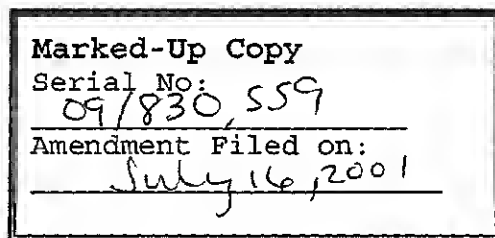
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ABSTRACT

A compound or a salt thereof having the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 , said atoms constitute the pharmacophore represented by the following formula:



and inhibits the activity of transcription factor AP-1 and is useful as an agent for preventing and treating the diseases into which over expression of AP-1 participates and as an AP-1 inhibitor.



IN THE CLAIMS

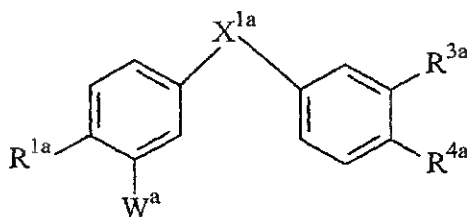
--3. (Amended) A compound or a salt thereof according to Claim 1 [or 2], wherein N₁ constituting the pharmacophore is a nitrogen atom of unsubstituted or substituted amino, ammonium, amido, thioamido, ureido, isoureido, amidino, guanidino, thioureido, hydrazino or hydrazono group to which one or more hydrogen atoms are bonded, a carbon atom of ethenyl group to which a hydrogen atom is bonded, an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfonyl group, an oxygen atom of sulfonyloxy group, an oxygen atom of sulfo group, an oxygen atom of sulfinyl group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, a sulfur atom of mercapto group, an oxygen atom of hydroxyl group, an oxygen atom of ester or a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group; N₂ is an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfo group, an oxygen atom of sulfonyl group, an oxygen atom of sulfo group, an oxygen atom of sulfonyloxy group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, an oxygen atom of hydroxyl group, an oxygen atom of ester, a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group to which no hydrogen atom is combined, a nitrogen atom of sulfonamido

09/830,559-050701

group or a nitrogen atom of acylsulfonamido group; and each of N₂, N₄ and N₅ is an arbitrary carbon atom constituting a carbon atom of alkyl group, a carbon atom of alkenyl group, a carbon atom of aryl group and a carbon atom of alkoxy group.

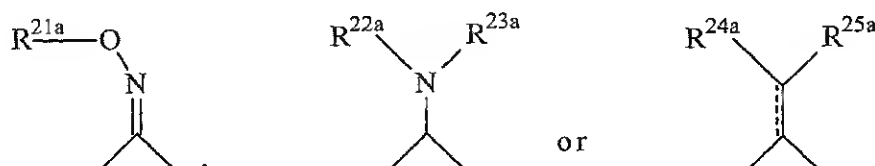
4. (Amended) A compound or a salt thereof according to [any one of Claims 1 to 3] Claim 1, wherein a compound having an atom corresponding to N₃ and atoms corresponding to two or more atoms selected from N₁, N₂, N₄ and N₅ among the atoms N₁, N₂, N₃, N₄ and N₅ constituting a pharmacophore, and, in the optimized three-dimensional structure thereof, the interatomic distances between the atom corresponding to N₃ and the two or more atoms selected from N₁, N₂, N₄ and N₅ are the atomic distances of a pharmacophore has an activity of antagonistically inhibiting the binding between AP-1 (activator protein-1) and a recognition sequence thereof.

16. (Amended) A benzene derivative represented by the following formula:



wherein R^{1a} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{3a} and R^{4a} may be the same or different represent a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a

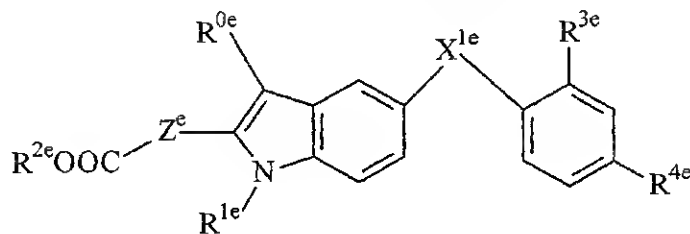
mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1a} represents $-C(O)-$, $-CH(OH)-$, $-CH_2-$ or a group of the following formula:



wherein R^{21a} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group; R^{22a} and R^{23a} may be the same or different represent a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, carbamoyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^{24a} and R^{25a} may be the same or different represent a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; and the double line of which one line is a broken line represents a single bond or a double bond and W^a represents $-Z^a-COR^{26a}$, $-Z^a-COOR^{2a}$, $-O-CH_2COOR^{2a}$ or $-O-CH_2CH_2COOR^{2a}$ (wherein Z^a represents $-(CH_2)_n-$ (n is [0,] 1, 2 or 3), $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; R^{2a} represents a hydrogen atom or a protecting group for carboxyl group; and R^{26a} represents $-NHR^{27a}$ or $-NHSO_2R^{28a}$ [in which] (R^{27a} and R^{28a} independently represent an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group));

or a salt thereof.

24. (Amended) A benzene derivative represented by the following general formula:

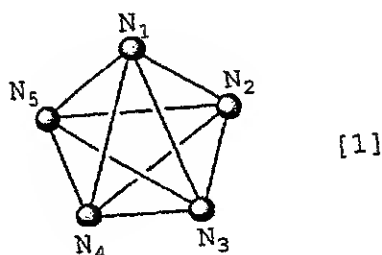


wherein R^{0e} represents a hydrogen atom, a halogen atom, a nitro group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonylamino or arylsulfonylamino group; R^{1e} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl group; R^{2e} represents a hydrogen atom or a protecting group for carboxyl group; R^{3e} and R^{4e} may be the same or different represent a hydrogen atom, a halogen atom, an unprotected or protected hydroxyl group, a unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group, provided that both R^{3e} and R^{4e} cannot simultaneously be a hydrogen atom; X^{1e} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^e represents $-(CH_2)_n-$ (n^e represents 0, 1 or 2) or $-CH=CH-$;

or a salt thereof.

29. (Amended) A compound or a salt thereof according to [any one of Claims 5 to 28] Claim 9, wherein said compound [according to any one of Claims 5 to 28] is a compound that has an activity of antagonistically inhibiting the combination between AP-1 and a recognition sequence thereof.

30. (Amended) [A compound or a salt thereof according to Claim 1] A compound comprising the atom corresponding to N₁ and the two or more atoms selected from N₁, N₂, N₄ and N₅, said atoms constitute the pharmacophore represented by the following formula 1:



wherein N₁ represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N₃ represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N₂, N₄ and N₅ independently represent an arbitrary carbon atom constituting a hydrophobic group and the distance between N₁ and N₂ is not less than 5 angstroms and not more than 12 angstroms, the distance between N₁ and N₃ is not less than 9 angstroms and not more than 15 angstroms, the distance between N₁ and N₄ is not less than 3 angstroms and not more than 13 angstroms, the distance between N₁ and N₅ is not less than 8 angstroms and not more than 16 angstroms, the distance between N₂ and N₃ is not less than 3 angstroms and not more than 10 angstroms, the distance between N₂ and N₄ is not less than 6 angstroms and not more than 14 angstroms, the distance between N₂ and N₅ is not less than 9 angstroms and not more than 14 angstroms, the distance between N₃ and N₄ is not less than 4 angstroms and not more than 11 angstroms, the distance between N₃ and N₅ is not less than 3 angstroms and not more than 10 angstroms, the distance between N₄ and N₅ is not less than 4 angstroms and not

more than 9 angstroms; and, in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; and a salt thereof, wherein the compound conforming to a pharmacophore [of Claim 1] is a peptide or a benzene derivative according to [any one of Claims 5 to 28] Claim 9.

31. (Amended) A method for inhibiting AP-1 which comprises administering a compound or a salt thereof according to [any one of Claims 1 to 30] Claim 1.

32. (Amended) An agent for preventing and treating a disease into which an excessive expression of AP-1 participates, which comprises a compound or a salt thereof according to [any one of Claims 1 to 30] Claim 1.

33. (Amended) An agent for preventing and treating an autoimmune disease, which comprises a compound or a salt thereof according to [any one of Claims 1 to 30] Claim 1.

34. (Amended) An AP-1 inhibitor comprising a compound or a salt thereof according to [any one of Claims 1 to 30] Claim 1.

Claims 35-40 (New).--

IN THE ABSTRACT

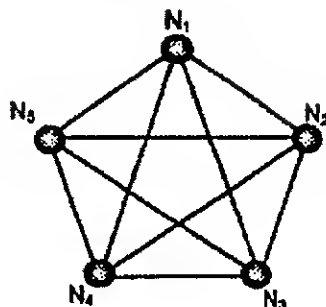
--New.--



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出願人 (米国を除くすべての指定国について) 化学工業株式会社 YAMA CHEMICAL CO., LTD. [JP/JP] 60-0023 東京都新宿区西新宿3丁目2-5 Tokyo, (JP) 発明者; および 発明者/出願人 (米国についてのみ) 久晃(CHAKI, Hisaaki)[JP/JP] 30-1328 富山県上新川郡大山町小原屋455-1 Toyama, (JP) 忠和(TAKAKURA, Tadakazu)[JP/JP] 39-8073 富山県富山市大町26-2 Toyama, (JP) 圭一(TSUCHIDA, Keiichi)[JP/JP] 39-2701 富山県婦負郡婦中町西本郷427-23 Toyama, (JP) 潤一(YOKOTANI, Junichi)[JP/JP] 30-0817 富山県富山市下奥井1-6-27 Toyama, (JP)	(81) 指定国 AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, 欧州特許 (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI特許 (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG), ARIPO特許 (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), ユーラシア特許 (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM) 添付公開書類 国際調査報告書	

Title: NOVEL COMPOUNDS AND MEDICINAL USE THEREOF

発明の名称 新規化合物およびその医薬用途



(I)

(57) Abstract

Compounds represented by formula (I) wherein N_1 represents an atom to which a donor hydrogen atom in a hydrogen bond donor group is bonded or a hydrogen bond acceptor atom in a hydrogen bond acceptor group; N_2 represents a hydrogen bond acceptor atom in a hydrogen bond acceptor group; and N_3 , N_4 and N_5 represent each an arbitrary carbon atom constituting a hydrophobic group, having an atom corresponding to N_3 and atoms corresponding to at least two atoms selected from N_1 , N_2 , N_4 and N_5 among the five atoms constituting a pharmacophore specified by the interatomic distances among N_1 , N_2 , N_3 , N_4 and N_5 ; and, in the optimized stereochemical structure thereof, the interatomic distances between the atom corresponding to N_3 and atoms corresponding to at least two atoms selected from N_1 , N_2 , N_4 and N_5 fall within the scope of the pharmacophore interatomic distance, or salts thereof. Because of having an effect of inhibiting the activity of a transcription factor AP-1, these compounds are useful as preventives/remedies for diseases in which the excessive expression of AP-1 participates and as AP-1 inhibitors.

Figure 6

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TGAGTCA-3') on genes, it exhibits a function as a transcription factor. As substances having such a sequence on the gene, proteins such as collagenases, stromelysin, metallothionein, interleukin-2 and the like and viruses such as SV40, polyoma virus and the like are known (Cell, Vol. 49, Pages 729-739, 1987).

Hitherto, as therapeutic drugs for may diseases, therapeutic drugs for controlling the function of proteins participating in the pathology such as enzymes and receptors have been developed. It is considered that, however, in the diseases caused by a quantitative abnormality of functional molecules existing in cells or on cell membranes, a treatment in the true sense is to control the quantity of transcription of the genes of the functional molecule and normalize the quantity of its expression rather than to control the activity of the functional molecules.

The gene expression and production of these functional proteins are controlled by a plurality of transcription factors. Since a transcription binding AP-1 sequence is common to exist in the promoter region of many genes, it is expected that various diseases may be effectively treated by controlling the AP-1 activity.

Up to today, it has been disclosed that glucocorticoids (Cell, Vol. 82. Pages 1189-1204, 1990) and retinoid derivatives (Nature, Vol. 372, Pages 107-

111, 1994) can suppress the activity of AP-1. The action mechanism is considered as follows at the present time. Thus, these substances can form a complex together with respective receptor, and
5 association of the complex with AP-1 can suppress of the binding of AP-1 to gene.

Steroidal agents used as therapeutic drugs for various diseases are known to exhibit a controlling action at the stage of expression of gene through
10 intermediation of a glucocorticoid receptor. In fact, it has been reported that steroidal agents inhibit the activity of AP-1 and suppresses the production of cytokines and other proteins (Cell, Vol. 62, Pages 1189-1204, 1990). On the other hand, the use of
15 steroidal agents are restricted from the viewpoint of hormone actions and side effects, and their side effects have a problem when they are administered excessively and/or for a long period of time.

In the recent years, a novel chemical drug is
20 usually developed by a rational drug design base on the three-dimensional structure of biopolymers such as proteins (e.g., receptors and enzymes) and nucleic acid, which play an important physiological role (Shin Seikagaku Jikken Koza, Vol. 13, Pages 291-337, Tokyo
25 Kagaku Dojin, 1993).

For applying this method, it is indispensably necessary to know the three-dimensional structure of the target bipolymer. The three-dimensional structure

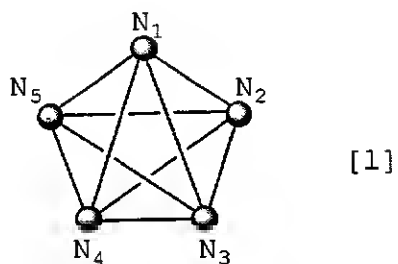
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of the complex of transcription factor AP-1 and the complexes of its binding sequence have been elucidated by X ray crystallographic analysis (Nature, Vol. 373, Pages 257-261, 1995).

5 Accordingly, it has been desired to develop an agent for prevention and/or treatment of diseases in which overexpression of AP-1 participates, which suppresses the excessive expression of a wide variety of genes on the basis of AP-1 inhibitory action with
10 lessened side reactions.

DISCLOSURE OF THE INVENTION

In the above-mentioned state of things, the present inventors have conducted extensive studies to find that compounds comprising the atom corresponding
15 to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 said atoms constitute the pharmacophore represented by the following formula:



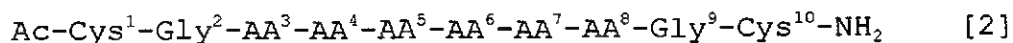
wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is
20 bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond

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accepting atom in a hydrogen bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, and the distance between N_4 and N_5 is not less than 4 angstroms and not more than 9 angstroms; and, in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; or salts thereof; inhibit activity on transcription factor AP-1, and are useful for prevention and treatment of diseases into which an overexpression of AP-1 participates. Further, it has also been found that specific compounds

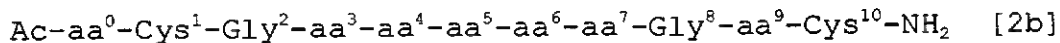
conforming to the above-mentioned definition of
 pharmacophore, having an inhibitory activity upon
 transcription factor AP-1 and useful as an agent for
 prevention and treatment of the diseases into which an
 5 overexpression of AP-1 participates include the
 following:

a peptide having 10 residues represented by
 the following amino acid sequence:



wherein Ac represents an acetyl group, AA³ represents a
 10 polar amino acid residue, AA⁴, AA⁶ and AA⁷ independently
 represent a hydrophobic amino acid residue, AA⁵
 represents an amino acid residue having carboxyl group
 or hydroxyl group on side chain thereof, and AA⁸
 represents an arbitrary amino acid residue; and having
 15 a disulfide linkage between the first and tenth
 cysteine residues; or salts thereof;

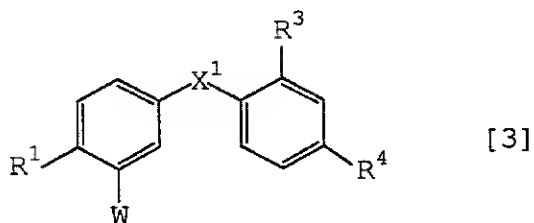
a peptide having 10 or 11 residues
 represented by the following amino acid sequence:



wherein Ac represents an acetyl group, aa⁰ represents an
 20 arbitrary amino acid residue or a bonding unit, aa³
 represents a polar amino acid residue, aa⁴, aa⁵ and aa⁷
 independently represent a hydrophobic amino acid

residue, aa⁶ represents an arbitrary amino acid residue,
 and aa⁹ represents an amino acid residue having carboxyl
 group or hydroxyl group on side chain thereof; provided
 that when aa⁰ is a bonding unit, a disulfide linkage
 5 exists between the 2nd and 11th cysteine residues; or
 salts thereof;

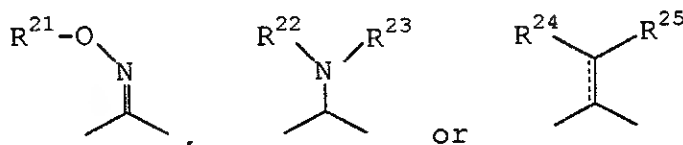
benzene derivatives represented by the
 following general formula:



wherein R¹ represents halogen atom, cyano group, nitro
 10 group, unprotected or protected hydroxyl group,
 unprotected or protected amino group, mercapto group or
 unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 15 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R³ represents halogen atom, cyano group, nitro
 group, unprotected or protected carboxyl group,
 unprotected or protected hydroxyl group, unprotected or
 20 protected amino group, mercapto group, carbamoyl group
 or unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,

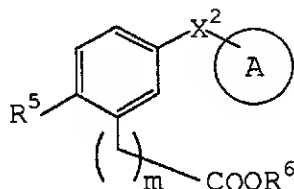
alkoxycarbonyl, aryloxycarbonyl, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R⁴ represents hydrogen atom, cyano group, nitro
 5 group, unprotected or protected carboxyl group,
 unprotected or protected hydroxyl group, unprotected or
 protected amino group, mercapto group or unsubstituted
 or substituted alkyl, alkenyl, cycloalkyl, aryl,
 aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl,
 10 aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl,
 alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group;

X¹ represents -C(O)-, -CH(OH)-, -CH₂- or a
 15 group of any one of the following formulas:



wherein R²¹ represents unsubstituted or substituted
 alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or
 heterocycle-lower alkyl group; R²² and R²³ may be the
 same or different and independently represent hydrogen
 20 atom, unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, acyl, carbamoyl,
 alkylsulfinyl, alkylsulfonyl, arylsulfonyl or
 heterocyclic group; R²⁴ and R²⁵ may be the same or

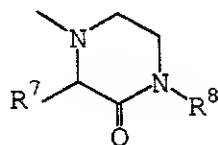
different and independently represent hydrogen atom,
 halogen atom, cyano group, nitro group, unprotected or
 protected carboxyl group, unprotected or protected
 hydroxyl group, unprotected or protected amino group,
 5 mercapto group or unsubstituted or substituted alkyl,
 alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy,
 acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl,
 alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino,
 acylamino, alkylsulfonylamino, arylsulfonylamino or
 10 heterocyclic group; and the double line in which one
 line is a broken line represents a single bond or a
 double bond; and W represents $-Z-COR^{26}$, $-Z-COOR^2$, $-O-$
 CH_2COOR^2 or $-O-CH_2CH_2COOR^2$, wherein Z is $-(CH_2)_n-$ (n is 0,
 1, 2 or 3), $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; R^2
 15 represents hydrogen atom or a protecting group for
 carboxyl group; and R^{26} represents $-NHR^{27}$ or $NHSO_2R^{28}$ (R^{27}
 and R^{28} independently represent unsubstituted or
 substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl
 group); or salts thereof;
 20 benzene derivatives represented by the
 following general formula:



[4]

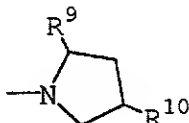
wherein R^5 represents hydrogen atom, halogen atom, cyano
 group, nitro group, unprotected or protected carboxyl

group, unprotected or protected hydroxyl group,
 unprotected or protected amino group, mercapto group or
 unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 5 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R^6 represents hydrogen atom or a protecting group
 for carboxyl group; X^2 represents $-C(O)-$; m represents
 10 0, 1 or 2; ring A represents a group represented by the
 following formula:



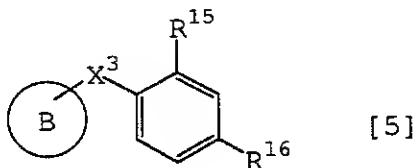
in which R^7 represents hydrogen atom, halogen atom,
 cyano group, nitro group, unprotected or protected
 carboxyl group, unprotected or protected hydroxyl
 15 group, unprotected or protected amino group, mercapto
 group or unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 20 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R^8 represents hydrogen atom, unprotected or
 protected amino group or unsubstituted or substituted
 alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy,

aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl,
 carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl,
 alkylamino, acylamino, alkylsulfonylamino,
 arylsulfonylamino or heterocyclic group; or a group
 5 represented by the following formula:

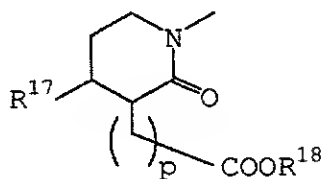


wherein R⁹ and R¹⁰ may be the same or different and
 independently represent halogen atom, cyano group,
 nitro group, unprotected or protected carboxyl group,
 unprotected or protected hydroxyl group, unprotected or
 10 protected amino group, mercapto group or unsubstituted
 or substituted alkyl, alkenyl, cycloalkyl, aryl,
 aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl,
 aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl,
 alkylsulfonyl, alkylamino, acylamino,
 15 alkylsulfonylamino, alkanoyloxy, arylsulfonylamino or
 heterocyclic group; or salts thereof;

benzene derivatives represented by the
 following formula:

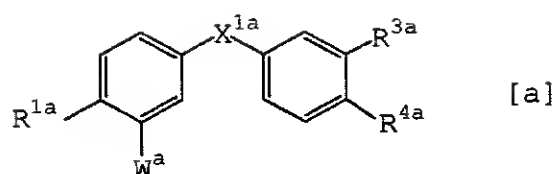


wherein R^{15} and R^{16} may be the same or different and independently represent hydrogen atom, halogen atom, cyano group, nitro group, unprotected or protected carboxyl group, unprotected or protected hydroxyl group, unprotected or protected amino group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^3 represents $-C(O)-$; and ring B represents a group of the following formula:

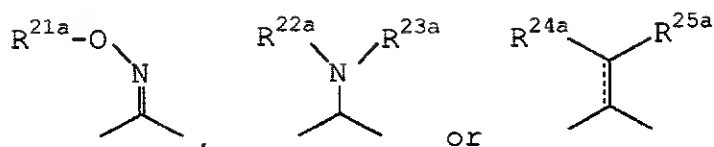


in which R^{17} represents hydrogen atom or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylsulfonyl or heterocyclic group; R^{18} represents hydrogen atom or a protecting group for carboxyl group; and p represents 0, 1 or 2; or salts thereof;

benzene derivatives represented by the following formula:



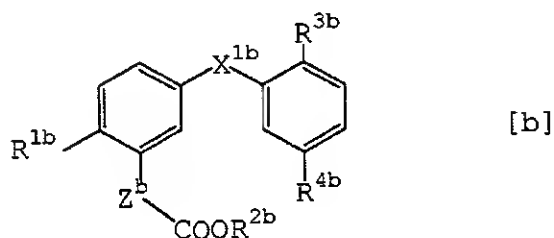
wherein R^{1a} represents halogen atom, cyano group, nitro group, unprotected or protected hydroxyl group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{3a} and R^{4a} may be the same or different and independently represent halogen atom, cyano group, nitro group, unprotected or protected carboxyl group, unprotected or protected hydroxyl group, unprotected or protected amino group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1a} represents $-C(O)-$, $-CH(OH)-$, $-CH_2-$ or a group of the following formula:



in which R^{21a} represents unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group; R^{22a} and R^{23a} may be the same or different and independently represent hydrogen atom, or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, carbamoyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; and R^{24a} and R^{25a} may be the same or different and independently represent hydrogen atom, halogen atom, cyano group, nitro group, unprotected or protected carboxyl group, unprotected or protected hydroxyl group, unprotected or protected amino group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; and the double line in which one line is a broken line represents a single bond or a double bond; and W^a represents $-\text{Z}^a-\text{COR}^{26a}$, $-\text{Z}^a-\text{COOR}^{2a}$, $-\text{O}-\text{CH}_2\text{COOR}^{2a}$ or $-\text{O}-\text{CH}_2\text{CH}_2\text{COOR}^{2a}$; in which Z^a represents $-(\text{CH}_2)_n^a$ (n^a represents 0, 1, 2 or 3), $\text{CH}_2\text{CH}(\text{CH}_3)-$, $-\text{CH}=\text{CH}-$ or $-\text{CH}_2\text{CH}=\text{CH}-$; R^{2a} represents hydrogen atom or a

protecting group for carboxyl group; and R^{26a} represents $-NHR^{27a}$ or $-NHSO_2R^{28a}$ (R^{27a} and R^{28a} independently represent unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group); or salts thereof;

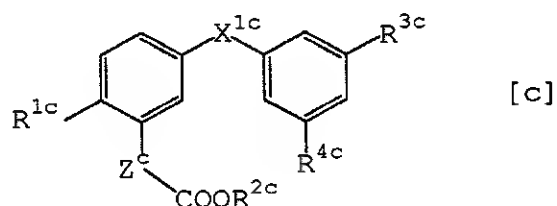
- 5 benzene derivatives represented by the following general formula:



- wherein R^{1b} represents halogen atom, cyano group, nitro group, unprotected or protected hydroxyl group, unprotected or protected amino group, mercapto group or
- 10 unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic
- 15 group; R^{2b} represents hydrogen atom or a protecting group for carboxyl group; R^{3b} and R^{4b} may be the same or different and independently represent cyano group, nitro group, unprotected or protected carboxyl group, unprotected or protected hydroxyl group, unprotected or
- 20 protected amino group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl,

aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl,
 alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; and X^{1b} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and
 5 Z^b represents $-(CH_2)_n-$ (n^b represents 0, 1 or 2) or $-$
 $CH=CH-$; or salts thereof;

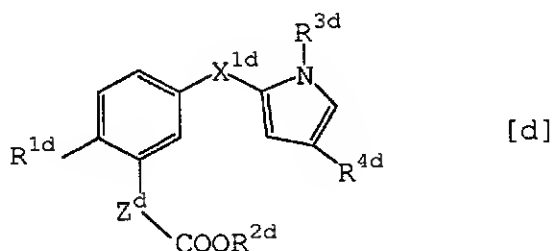
benzene derivatives represented by the
 following general formula:



wherein R^{1c} represents halogen atom, cyano group, nitro
 10 group, unprotected or protected hydroxyl group,
 unprotected or protected amino group, mercapto group or
 unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 15 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R^{2c} represents hydrogen atom or a protecting
 group for carboxyl group; R^{3c} and R^{4c} may be the same or
 different and independently represent halogen atom,
 20 cyano group, nitro group, unprotected or protected
 carboxyl group, unprotected or protected hydroxyl
 group, unprotected or protected amino group, mercapto

group or unsubstituted or substituted alkenyl,
 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 5 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; X^{1c} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^c
 represents $-(CH_2)_n-$ (n^c represents 0, 1 or 2) or $-CH=CH-$
 ; or salts thereof;

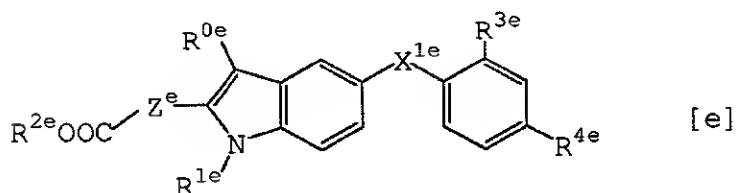
benzene derivatives represented by the
 10 following general formula:



wherein R^{1d} represents halogen atom, cyano group, nitro
 group, unprotected or protected hydroxyl group,
 unprotected or protected amino group, mercapto group or
 unsubstituted or substituted alkyl, alkenyl,
 15 cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl,
 alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio,
 alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino,
 alkylsulfonylamino, arylsulfonylamino or heterocyclic
 group; R^{2d} represents hydrogen atom or a protecting
 20 group for carboxyl group; R^{3d} represents hydrogen atom
 or unsubstituted or substituted alkyl, alkenyl,
 cycloalkyl, aryl or aralkyl group; R^{4d} represents alkyl,

5 $-(\text{CH}_2)_{n^d}-$ (n^d represents 0, 1 or 2) or $-\text{CH}=\text{CH}-$; or salts thereof;

benzene derivatives represented by the following general formula:

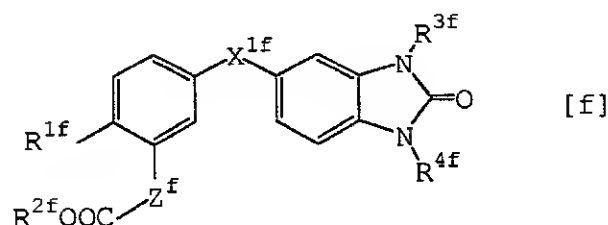


wherein R^{0e} represents hydrogen atom, halogen atom,
10 nitro group or unsubstituted or substituted alkyl,
alkenyl, cycloalkyl, aryl, aralkyl, acyl,
alkoxycarbonyl, aryloxycarbonyl, alkylsulfonylamino or
arylsulfonylamino group; R^{1e} represents unsubstituted or
substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
15 acyl, alkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl
group; R^{2e} represents hydrogen atom or a protecting
group for carboxyl group; R^{3e} and R^{4e} may be the same or
different and independently represent hydrogen atom,
halogen atom, unprotected or protected hydroxyl group,
20 unprotected or protected amino group, mercapto group or
unsubstituted or substituted alkyl, alkenyl,
cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio,
alkylamino, acylamino, alkylsulfonylamino,

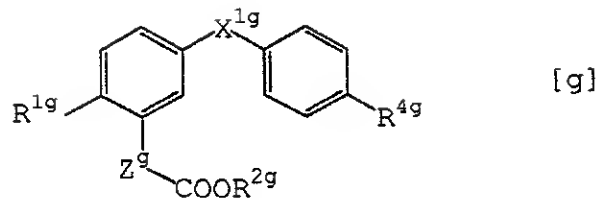
arylsulfonylamino or heterocyclic group; X^{1e} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^e represents $-(CH_2)_{n^e}-$ (n^e represents 0, 1 or 2) or $-CH=CH-$; or salts thereof;

benzene derivatives represented by the

5 following general formula:



wherein R^{1f} represents halogen atom, unprotected or protected hydroxyl group, unprotected or protected amino group, mercapto group or unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio, alkylamino, acylamino, 10 alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{2f} represents hydrogen atom or a protecting group for carboxyl group; R^{3f} and R^{4f} may be the same or different and independently represent hydrogen atom or 15 unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group; X^{1f} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^f represents $-(CH_2)_{n^f}-$ (n^f represents 1 or 2) or $-CH=CH-$; or salts thereof; and benzene derivatives represented by the 20 following general formula:



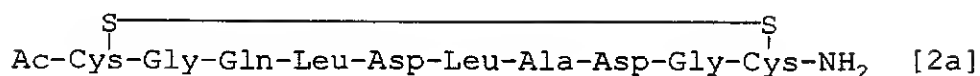
wherein R^{1g} and R^{4g} may be the same or different and independently represent unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group; X^{1g} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; Z^g represents $-(CH_2)_n-$ (n^g represents 1 or 2); and R^{2g} represents hydrogen atom or a protecting group for carboxyl group; or salts thereof;

and agents comprising the above-mentioned compounds.

Based on these findings, this invention has been accomplished.

First, the present inventors took out only the three-dimensional structure of transcription factor AP-1 from the three-dimensional structure of a partial structure containing the DNA binding site of AP-1 and its binding sequence (oligonucleotide containing 5'-TGAGTCA-3') (Nature, Vol. 373, Pages 257-261, 1995) by using the molecular modeling software "SYBYL" (TRIPOS Co., USA), and searched for a compound binding to AP-1 and antagonistic to the AP-1 binding sequence. As its result, it was found that a peptide of the following

formula:



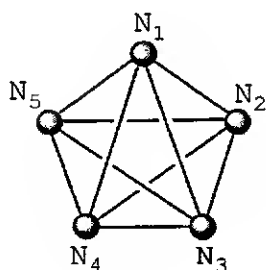
can bind to with AP-1 and have an antagonistic activity to the AP-1 binding sequence.

Subsequently, a three-dimensional structure of a complex compound of peptide [2a] and a partial structure containing the DNA binding site of AP-1 were prepared by the use of SYBYL, and a molecular dynamics simulation was carried out according to the molecular dynamics calculation program AMBER (Oxford Molecular Co., GB) (Fundamentals of Protein Engineering Physics and Chemistry, published by Kyoritsu Shuppan, Page 192, 1991) by using the three-dimensional structure obtained above as an initial structure to obtain a plurality of three-dimensional structures of AP-1-cyclic peptide [2a] complex in water.

On the other hand, nuclear magnetic resonance (NMR) spectrum of peptide [2a] was measured, and the result was treated according to a structural analysis software X-PLOR (MSI Co., USA) to obtain a plurality of three-dimensional structures of peptide [2a] in water experimentally (Shinsei Kagaku Jikken Koza I, Proteins III, Pages 139-147, 1990, published by Tokyo Kagaku Dojin).

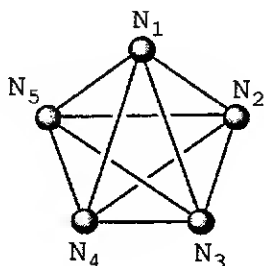
The experimentally obtained three-dimensional structures were compared with the three-dimensional

structures of cyclic peptide [2a] in the complex obtained from the molecular dynamics simulation. As a result, a high level of similarity was found out between eleven of the experimentally confirmed three-dimensional structures and fourteen of the three-dimensional structures obtained from molecular dynamics simulation in the partial three-dimensional structure of Gln-Leu-Asp-Leu-Ala. Based on this finding, it could be confirmed that the five atoms N_1 , N_2 , N_3 , N_4 and N_5 expressed by the following formula:



wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group, constitute a pharmacophore necessary for the binding to AP-1 and the expression of an antagonistic activity to AP-1 binding sequence (Souyaku Kagaku, Kagaku Dojin, Pages 11-13, 1995).

Further, distances between five atoms N_1 , N_2 , N_3 , N_4 and N_5 , which are selected therefrom in these 25 three-dimensional structures, and which constitute the pharmacophore necessary for the binding to AP-1 and the expression of the antagonistic activity to AP-1 binding sequence were measured. As N_1 , the nitrogen atom or oxygen atom of amide group was taken into consideration. As N_2 , the four carbon atoms of isobutyl group were taken into consideration. As N_3 , the two oxygen atoms of carboxyl group were taken into consideration. As N_4 , the four carbon atoms of isobutyl group were taken into consideration. As N_5 , the carbon atom of methyl group was taken into consideration. On all the possible combinations of the five atoms, distances were measured. As a result, it was found that the condition represented by the following formula:

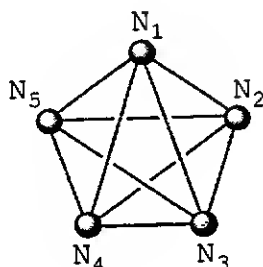


wherein N_1 represents an atom to which to a donative hydrogen atom in the hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in the hydrogen-bond accepting group, N_3 represents a hydrogen-

bond accepting atom in the hydrogen-bond accepting group, and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group, and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, and the distance between N_4 and N_5 is not less than 4 angstroms and not more than 9 angstroms are necessary for binding to AP-1 and expressing the antagonistic activity to AP-1 binding sequence. Based on these findings, the pharmacophore model was completed.

Further, compounds conforming to the above-mentioned pharmacophore model were extensively searched to find out non-peptide compounds which can bind to AP-1 and have the antagonistic activity to AP-1 binding

sequence. It was found that compounds comprising the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 , said atoms constitute the pharmacophore represented by the following formula:



- 5 wherein N_1 represents an atom bonded to a donative hydrogen atom in the hydrogen-bond donating group or a hydrogen-bond accepting atom in the hydrogen-bond accepting group, N_3 represents a hydrogen-bond accepting atom in the hydrogen bond-accepting group, and N_2 , N_4
- 10 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group, and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15
- 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10
- 20 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the

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distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, and the distance between N_4 and N_5 is not less than 4 angstroms and not more than 9 angstroms, and in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; or salts thereof inhibit the activity of transcription factor AP-1 and are useful as an agent for preventing and treating the diseases into which overexpression of AP-1 participates.

The compounds of this invention inhibit the binding activity of transcription factor AP-1. That is, the compounds of this invention antagonistically inhibit the bind of AP-1 to the AP-1-recognizing sequence on DNA, and thereby suppress the transcription of AP-1-related DNA, and thereby can reduce the expression of protein corresponding to said genes having AP-1 binding sequence. Accordingly, the compounds of this invention can suppress the expression of gene in tissue-destroying enzymes such as collagenase, stromelysin, gelatinases and the like; cytokines such as interleukin-1, interleukin-2, interleukin-3, interleukin-6, interleukin-8, TNF α ,

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granulocyte-macrophage colony stimulating factor (GM-CSF), monocyte chemotactic factor (MCP-1) and the like; cell surface molecule groups such as interleukin-2 receptor, immunoglobulins, major histocompatibility complex (MHC) class II, vascular cell adhesion molecule-1 (VCAM-1), fibroblast growth factor (FGF) receptors and the like; growth factors such as monocyte growth factor, insulin-like growth factor (IGF), nervous growth factor (NGF) and the like; proteins such as metallothionein, collagens, osteocalcin, amyloid precursor proteins, apolipoprotein-1 and the like; and viruses such as SV40, polyoma virus and the like, and thereby can prevent and treat the diseases related with these genes. As the diseases to which these genes relate, for instance, various autoimmune diseases such as rheumatoid arthritis, systemic erythematosus, scleroderma, Behchet's disease, rheumatic fever, polymyositis, polyarteritis nodosa, Sjogren's syndrome, active chronic hepatitis, glomerulonephritis and the like; various intractable diseases basically with inflammations such as osteoarthritis, gout, atherosclerosis, psoriasis, atopic dermatitis, lung diseases with granuloma, various encephalitis, and the like; lung diseases with granuloma such as pneumonitis; endotoxin shock; sepsis; inflammatory colitis; diabetes mellitus; acute myeloblastic leukemia; encephalomyelitis; acute hepatitis; chronic hepatitis; drug-induced hepatitis; alcoholic hepatitis; viral

hepatitis; jaundice; cirrhosis; liver failure; atrial myxoma; Castleman's syndrome; multiple myeloma; cancer; metastases of cancer; AIDS; epilepsy; ischemic heart disease; hemangio-endothelial hyperplasia

- 5 (arteriosclerosis); Alzheimer's disease; ischemia-nerve cell death; etc. The compounds of this invention are expected to be effective for prevention and treatment of these diseases.

The compounds of this invention will be
10 detailed below.

Unless otherwise defined, the term "halogen atom" used in this specification means fluorine atom, chlorine atom, bromine atom and iodine atom; "alkyl group" means straight or branched chain C₁₋₁₂ alkyl
15 groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl, hexyl, heptyl, octyl and the like; "lower alkyl group" means straight or branched chain C₁₋₆ alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-
20 butyl, sec-butyl, isobutyl, tert-butyl, pentyl, isopentyl and the like; "halogeno lower alkyl group" means straight or branched chain halogeno-C₁₋₆ alkyl groups such as fluoromethyl, chloromethyl, bromomethyl, dichloromethyl, trifluoromethyl, trichloromethyl,
25 chloroethyl, dichloroethyl, trichloroethyl, chloropropyl and the like; "lower alkoxy lower alkyl group" means straight or branched chain C₁₋₆ alkoxy-C₁₋₆ alkyl groups such as methoxymethyl, ethoxymethyl, n-

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propoxymethyl, methoxyethyl, ethoxyethyl and the like;
 "hydroxy lower alkyl group" means straight or branched
 chain hydroxy-C₁₋₆ alkyl groups such as hydroxymethyl,
 hydroxyethyl, hydroxypropyl and the like; "amino lower
 5 alkyl group" means amino-C₁₋₆ alkyl groups such as
 aminomethyl, aminoethyl, aminopropyl and the like;

"alkenyl group" means straight or branched
 chain C₂₋₁₂ alkenyl groups such as vinyl, allyl,
 propenyl, isopropenyl, butenyl, isobutenyl, pentenyl,
 10 hexenyl, heptenyl, octenyl and the like; "lower alkenyl
 group" means straight or branched chain C₂₋₆ alkenyl
 groups such as vinyl, allyl, propenyl, isopropenyl,
 butenyl, isobutenyl, pentenyl and the like; "cycloalkyl
 group" means C₃₋₆ cycloalkyl groups such as cyclopropyl,
 15 cyclobutyl, cyclopentyl, cyclohexyl and the like; "ar-
 lower alkyl group" means ar-C₁₋₆ alkyl groups such as
 benzyl, diphenylmethyl, trityl, phenethyl and the like;

"aryl group" means phenyl, tolyl, naphthyl
 and the like; "aralkyl group" means benzyl,
 20 diphenylmethyl, trityl, phenethyl, 4-methylbenzyl,
 naphthylmethyl and the like; "aryloxy group" means
 phenoxy, naphthoxy and the like; "aryloxycarbonyl
 group" means phenoxycarbonyl, naphthoxycarbonyl and the
 like;

25 "alkoxy group" means straight or branched
 chain C₁₋₁₂ alkoxy groups such as methoxy, ethoxy, n-
 propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy,
 tert-butoxy, pentyloxy, isopentyloxy, hexyloxy,

heptyloxy, octyloxy and the like; "lower alkoxy group" means straight or branched chain C_{1-6} alkoxy groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, tert-butyloxy, pentyloxy,

- 5 isopentyloxy and the like; "alkoxycarbonyl group" means straight or branched chain C_{1-12} alkoxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, pentyloxycarbonyl and the like; "lower alkoxy carbonyl group" means straight or branched chain C_{1-6} alkyloxycarbonyl groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl and the like;

"lower alkoxycarbonyl lower alkyl group"

- 15 means straight or branched chain C_{1-6} alkoxycarbonyl- C_{1-6} alkyl groups such as methoxycarbonylmethyl, ethoxycarbonylmethyl, n-propoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl and the like; "lower alkoxyimino group" means straight or branched
- 20 chain C_{1-6} alkoxyimino groups such as methoxyimino, ethoxyimino and the like; "alkylamino group" means straight or branched chain C_{1-12} alkylamino groups such as methylamino, ethylamino, propylamino, butylamino, pentylamino, hexylamino, heptylamino, octylamino and
- 25 the like; "lower alkylamino group" means straight or branched chain mono- or di- C_{1-6} alkylamino groups such as methylamino, ethylamino, propylamino, dimethylamino, diethylamino, methylethylamino and the like; "lower

alkylamino lower alkyl group" means mono- or di-C₁₋₆ alkylamino-C₁₋₆ alkyl groups such as methylaminomethyl, methylaminoethyl, ethylaminomethyl, methylaminopropyl, propylaminoethyl, dimethylaminomethyl, diethylamino-

5 methyl, diethylaminoethyl, dimethylaminopropyl and the like; "lower alkylidene group" means C₁₋₆ alkylidene groups such as methylene, ethylidene, propylidene, isopropylidene and the like;

"acyl group" inclusively means straight or

10 branched chain C₂₋₁₂ alkanoyl groups such as formyl, acetyl, isovaleryl, propionyl and the like, aralkylcarbonyl groups such as benzylcarbonyl and the like, aroyl groups such as benzoyl, naphthoyl and the like, and heterocycle-carbonyl groups such as

15 nicotinoyl, thenoyl, pyrrolidinocarbonyl, furoylcarbonyl and the like; "acylamino group" means C₁₋₆ acylamino groups such as formylamino, acetylamino, propionylamino, butyrylamino and the like; "alkanoyloxy group" means C₂₋₁₂ alkanoyloxy groups such as acetyloxy,

20 propionyloxy and the like;

"cyclic amino group" may be any of saturated cyclic amino groups and unsaturated cyclic amino groups, and may contain one or more hetero atoms such as nitrogen atoms, oxygen atoms, sulfur atoms and the

25 like and carbonyl carbon atoms additionally in the ring thereof, and may be any of monocyclic, bicyclic and tricyclic groups, which more specifically include saturated or unsaturated, monocyclic, 3- to 7-membered

25

hexan-3-yl, 2-oxa-5,8-diazabicyclo[4.3.0]nonan-8-yl,
2,8-diazaspiro[4.4]nonan-2-yl, 7-
azabicyclo[2.2.1]heptan-7-yl and the like;

- "alkylthio group" means straight or branched
5 chain C_{1-12} alkylthio groups such as methylthio,
ethylthio, n-propylthio, isopropylthio, n-butylthio,
isobutylthio, sec-butylthio, tert-butylthio,
pentylthio, isopentylthio, hexylthio, heptylthio,
octylthio and the like; "lower alkylthio group" means
10 straight or branched chain C_{1-6} alkylthio groups such as
methylthio, ethylthio, n-propylthio, isopropylthio, n-
butylthio, isobutylthio, sec-butylthio, tert-butylthio,
pentylthio, isopentylthio and the like; "alkylsulfinyl
group" means straight or branched chain C_{1-12}
15 alkylsulfinyl groups such as methylsulfinyl,
ethylsulfinyl, n-propylsulfinyl, isopropylsulfinyl, n-
butylsulfinyl, isobutylsulfinyl, sec-butylsulfinyl,
tert-butylsulfinyl, pentylsulfinyl, isopentylsulfinyl,
hexylsulfinyl, heptylsulfinyl, octylsulfinyl and the
20 like; "alkylsulfonyl group" means straight or branched
chain C_{1-12} alkylsulfonyl groups such as methylsulfonyl,
ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-
butylsulfonyl, isobutylsulfonyl, sec-butylsulfonyl,
tert-butylsulfonyl, pentylsulfonyl, isopentylsulfonyl,
25 hexylsulfonyl, heptylsulfonyl, octylsulfonyl and the
like; "alkylsulfonylamino group" means straight or
branched chain C_{1-12} alkylsulfonylamino groups such as
methylsulfonylamino, ethylsulfonylamino, n-

propylsulfonylamino, isopropylsulfonylamino, n-butylsulfonylamino, isobutylsulfonylamino, sec-butylsulfonylamino, tert-butylsulfonylamino, pentylsulfonylamino, isopentylsulfonylamino, -

- 5 hexylsulfonylamino, heptylsulfonylamino, octylsulfonylamino and the like; "arylsulfonylamino group" means aryl-SO₂NH- groups such as phenylsulfonylamino, naphthylsulfonylamino and the like; and

- 10 "heterocycle-lower alkyl group" means heterocycle-CH₂- group and the like such as pyrrolidinylmethyl, piperidylmethyl, piperazinylmethyl, pyrazolylmethyl, tetrahydropyridylmethyl, morpholinylmethyl, thiomorpholinylmethyl, tetrahydro-
- 15 quinolinylmethyl, tetrahydroisoquinolinylmethyl, quinacridinylmethyl, tetrazolylmethyl, thiadiazolylmethyl, pyrazolidinylmethyl, purinylmethyl, indazolylmethyl, 2-thienylmethyl, 2-furfurylmethyl, 2-pyranylmethyl, 1-isobenzofurylmethyl, 2-pyrrolylmethyl,
- 20 1-imidazolylmethyl, 1-pyrazolylmethyl, 3-isothiazolylmethyl, 3-isoxazolylmethyl, 2-pyridylmethyl, 2-pyrazinylmethyl, 2-pyrimidinylmethyl, 2-pyridazinylmethyl, 1-isoindolylmethyl, 2-indolylmethyl, 1-isoquinolylmethyl, 2-quinolylmethyl,
- 25 1-phthalazinylmethyl, 2-naphthyridinylmethyl, 2-quinoxalinylmethyl, 2-quinazolinylmethyl, 3-cinnolinylmethyl, 2-oxazolylmethyl, 2-thiazolylmethyl, 2-benzo[b]furylmethyl, 2-benzo[b]thienylmethyl, 2-

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benz[d]imidazolylmethyl, 2-benz[d]oxazolylmethyl and the like.

"Nitrogen-containing heterocyclic group"

means 5- or 6-membered ring, fused ring or crosslinked
5 ring type heterocyclic groups which contain at least
one nitrogen atoms as hetero atoms constituting the
ring and may contain at least one oxygen atom or sulfur
atom in addition to said nitrogen atoms, such as
pyrrolyl, pyrrolidinyl, piperidyl, piperazinyl,
10 imidazolyl, pyrazolyl, pyridyl, tetrahydropyridyl,
pyrimidinyl, morpholinyl, thiomorpholinyl, quinolyl,
quinolizinyll, tetrahydroquinolinyl, tetrahydro-
isoquinolinyl, quinacridinyl, thiazolyl, tetrazolyl,
thiadiazolyl, pyrrolinyl, imidazolinyl, imidazolidinyl,
15 pyrazolinyl, pyrazolidinyl, purinyl, indazolyl and the
like; and "heterocyclic group" inclusively means the
above-mentioned nitrogen-containing heterocyclic groups
and 5- or 6-membered ring, fused ring or crosslinked
ring type heterocyclic groups which may contain at
20 least one oxygen atoms or sulfur atoms as hetero atoms
constituting the ring and contain at least one hetero
atom selected from the group consisting of nitrogen,
oxygen and sulfur atoms, such as furyl, thienyl,
benzothienyl, pyranlyl, isobenzofuranyl, oxazolyl,
25 benzofuranyl, indolyl, benzimidazolyl, benzoxazolyl,
benzothiazolyl, quinoxalyl, dihydroquinoxalinyll, 2,3-
dihydrobenzothienyl, 2,3-dihydrobenzopyrrolyl, 2,3-
dihydro-4H-1-thianaphthyl, 2,3-dihydrobenzofuranyl,

benzo[b]dioxanyl, imidazo[2.3-a]pyridyl,
benzo[b]piperazinyll, chromenyl, isothiazolyl,
isoxazolyl, thiadiazolyl, oxadiazolyl, pyridazinyll,
isoindolyl, isoquinolyl and the like.

5 As the protecting group for carboxyl group, all the groups which can conventionally be used as a protecting group for carboxyl group can be referred to. Examples thereof include alkyl groups such as methyl, ethyl, n-propyl, iso-propyl, 1,1-dimethylpropyl, n-
10 butyl, tert-butyl and the like; aryl groups such as phenyl, naphthyl and the like; aralkyl groups such as benzyl, diphenylmethyl, trityl, p-nitrobenzyl, p-methoxybenzyl, bis(p-methoxyphenyl)methyl and the like; acyl-alkyl groups such as acetylmethyl, benzoylmethyl, p-
15 p-nitrobenzoylmethyl, p-bromobenzoylmethyl, p-methanesulfonylbzoylmethyl and the like; oxygen-containing heterocyclic groups such as 2-tetrahydropyranyl, 2-tetrahydrofuranlyl and the like; halogeno-alkyl groups such as 2,2,2-trichloroethyl and
20 the like; alkylsilylalkyl groups such as 2-(trimethylsilyl)ethyl and the like; acyloxyalkyl groups such as acetoxymethyl, propionyloxymethyl, pivaloyloxymethyl and the like; nitrogen-containing heterocycle-alkyl groups such as phthalimidomethyl, succinimidomethyl and the like; cycloalkyl groups such
25 as cyclohexyl and the like; alkoxy-alkyl groups such as methoxymethyl, methoxyethoxymethyl, 2-(trimethylsilyl)-ethoxymethyl and the like; ar-alkoxy-alkyl groups such

as benzyloxymethyl and the like; alkylthio-alkyl groups such as methylthiomethyl, 2-methylthioethyl and the like; arylthioalkyl groups such as phenylthiomethyl and the like; alkenyl groups such as 1,1-dimethyl-2-propenyl, 3-methyl-3-butenyl, allyl and the like; and substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl, diethylisopropylsilyl, tert-butyl dimethylsilyl, tert-butyl diphenylsilyl, diphenylmethylsilyl, tert-butyl methoxyphenylsilyl and the like.

As the protecting group for amino group, all the groups which can conventionally be used as a protecting group for amino group can be referred to. Examples thereof include acyl groups such as trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, o-bromobenzyloxycarbonyl, (mono-, di- and tri-)chloroacetyl, trifluoroacetyl, phenylacetyl, formyl, acetyl, benzoyl, tert-amyl oxycarbonyl, tert-butoxycarbonyl, p-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 4-(phenylazo)-benzyloxycarbonyl, 2-furfuryloxycarbonyl, diphenylmethoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, phthaloyl, succinyl, alanyl, leucyl, 1-adamantyloxycarbonyl, 8-quinolyloxycarbonyl and the like; aralkyl groups such as benzyl, diphenylmethyl, trityl and the like; arylthio groups such as 2-nitrophenylthio, 2,4-dinitrophenylthio and

the like; alkyl- or aryl-sulfonyl groups such as methanesulfonyl, p-toluenesulfonyl and the like; dialkylamino-alkylidene groups such as N,N-dimethylaminomethylene and the like; aralkylidene groups such as benzylidene, 2-hydroxybenzylidene, 2-hydroxy-5-chlorobenzylidene, 2-hydroxy-1-naphthylmethylene and the like; nitrogen-containing heterocyclic alkylidene groups such as 3-hydroxy-4-pyridylmethylene and the like; cycloalkylidene groups such as cyclohexylidene, 2-ethoxycarbonylcyclohexylidene, 2-ethoxycarbonylcyclopentylidene, 2-acetylcyclohexylidene, 3,3-dimethyl-5-oxycyclohexylidene and the like; diaryl- or dialkylphosphoryl groups such as diphenylphosphoryl, dibenzylphosphoryl and the like; oxygen-containing heterocyclic alkyl groups such as 5-methyl-2-oxo-2H-1,3-dioxol-4-yl-methyl and the like; and substituted silyl groups such as trimethylsilyl and the like.

As protecting group for hydroxyl group, all the groups which can conventionally be used as a protecting group for hydroxyl group can be referred to. Examples thereof include acyl groups such as benzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 4-bromobenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, 1,1-dimethylpropoxycarbonyl, isopropoxycarbonyl, isobutyloxycarbonyl, diphenylmethoxycarbonyl, 2,2,2-

trichloroethoxycarbonyl, 2,2,2-tribromoethoxycarbonyl, 2-(trimethylsilyl)ethoxycarbonyl, 2-(phenylsulfonyl)-ethoxycarbonyl, 2-(triphenylphosphonio)ethoxycarbonyl, 2-furfuryloxycarbonyl, 1-adamantyloxycarbonyl,

5 vinyloxycarbonyl, allyloxycarbonyl, S-benzylthiocarbonyl, 4-ethoxy-1-naphthyloxycarbonyl, 8-quinolyloxycarbonyl, acetyl, formyl, chloroacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl, methoxyacetyl, phenoxyacetyl, pivaloyl, benzoyl and the

10 like; alkyl groups such as methyl, tert-butyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl and the like; alkenyl groups such as allyl and the like; aralkyl groups such as benzyl, p-methoxybenzyl, 3,4-dimethoxybenzyl, diphenylmethyl, trityl and the like;

15 oxygen-containing and sulfur-containing heterocyclic groups such as tetrahydrofuryl, tetrahydropyranyl, tetrahydrothiopyranyl and the like; alkoxy-alkyl groups such as methoxymethyl, methylthiomethyl, benzyloxymethyl, 2-methoxyethoxymethyl, 2,2,2-

20 trichloroethoxymethyl, 2-(trimethylsilyl)ethoxymethyl, 1-ethoxyethyl and the like; alkyl- and aryl-sulfonyl groups such as methanesulfonyl, p-toluenesulfonyl and the like; and substituted silyl groups such as trimethylsilyl, triethylsilyl, triisopropylsilyl,

25 diethylisopropylsilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, diphenylmethylsilyl, tert-butyloxymethoxyphenylsilyl and the like.

The term "amino acid residue" means a

structure -NHCHRCO- which appears when an amino acid is incorporated into a protein or peptide while forming a peptide bond with loss of a water molecule, wherein R represents an amino acid side chain. As used herein,

5 the term "amino acid" means an L-amino acid and a D-amino acid, namely compounds having carboxyl group and amino group in one molecule, unless otherwise defined. Examples of said amino acid include glycine, alanine, valine, leucine, isoleucine, serine, threonine,

10 asparagine, aspartic acid, glutamine, glutamic acid, lysine, arginine, histidine, methionine, tyrosine, phenylalanine, tryptophan, proline, cysteine, homocysteine, β -alanine, γ -aminobutyric acid, ornithine, 3,4-dihydroxyphenylalanine and the like.

15 For expression of amino acids and amino acid residues, the three letters expression prescribed by IUPAC and IUB is used.

The term "polar amino acid", means amino acids such as asparagine, glutamine, aspartic acid,

20 glutamic acid, serine, threonine, tyrosine, lysine, arginine, histidine, citrulline, homocitrulline, homoserine, hydroxyproline, β -hydroxyvaline, ornithine and the like, for example.

The term "hydrophobic amino acid" means amino

25 acids such as leucine, isoleucine, valine, alanine, glycine, methionine, proline, phenylalanine, tryptophan, norleucine, norvaline, γ -aminobutyric acid, β -cyclohexylalanine and the like, for example.

As the salt of compound in the compound conforming to the pharmacophore of formula 1, the compounds of general formulas [2], [2b], [3], [4], [5], [a], [b], [c], [d], [e], [f] and [g] or salts thereof, conventionally known salts at the site of basic group such as amino group and the like and conventionally known salts at the site of acidic group such as hydroxyl group, carboxyl group and the like can be referred to. As the salts at the site of basic group, for example, salts of mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid and the like, salts of organic carboxylic acids such as tartaric acid, formic acid, citric acid, trichloroacetic acid, trifluoroacetic acid and the like, and salts of sulfonic acids such as methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, mesitylenesulfonic acid, naphthalenesulfonic acid and the like can be referred to. As the salts at the site of acidic group, for example, salts of alkali metals such as sodium, potassium and the like, salts of alkaline earth metals such as calcium, magnesium and the like, ammonium salts, and salts of nitrogen-containing organic bases such as trimethylamine, triethylamine, tributylamine, pyridine, N,N-dimethylaniline, N-methylpiperidine, N-methylmorpholine, diethylamine, dicyclohexylamine, procaine, dibenzylamine, N-benzyl- β -phenethylamine, N,N'-dibenzylethylenediamine and the like can be

referred to. Further, among the salts mentioned above, preferable salts of the compound conforming to the pharmacophore of formula 1 and the compounds of formulas [2], [2b], [3], [4], [5], [a], [b], [c], [d], [e], [f] and [g], pharmacologically acceptable ones can be referred to.

As the "atom to which a donative hydrogen atom in the hydrogen-bond donating group is bonded", the nitrogen atom of unsubstituted or substituted amino, ammonium, amido, thioamido, ureido, isoureido, amidino, guanidino, thioureido, hydrazino or hydrazono group to which one or more hydrogen atoms are bonded, the carbon atom of ethenyl group to which a hydrogen atom is bonded, the nitrogen atom of imino group to which a hydrogen atom is bonded, the oxygen atom of hydroxyl group, the nitrogen atom to which the hydrogen atom of an unsubstituted or substituted nitrogen-containing heterocyclic group is bonded, and the like can be referred to.

The "hydrogen-bond accepting atom in hydrogen-bond accepting group" may be any atom, so far as it has an unshared electron pair. Examples thereof include the oxygen atom of carbonyl group, the sulfur atom of thiocarbonyl group, the nitrogen atom of unsubstituted or substituted imino group, the oxygen atom of sulfonic group, the oxygen atom of sulfonyl group, the oxygen atom of sulfinyl group, the oxygen atom of sulfonyloxy group, the oxygen atom of carboxyl

group, the oxygen atom of ether, the sulfur atom of thioether, the oxygen atom of hydroxyl group, the oxygen atom of ester, the nitrogen atom to which no hydrogen atom is bonded in an unsubstituted or

5 substituted nitrogen-containing heterocyclic group, the nitrogen atom of sulfonamido group, the nitrogen atom of acylsulfonamido group, etc.

As the "arbitrary carbon atom constituting a hydrophobic group", the carbon atom of alkyl group, the carbon atom of alkenyl group, the carbon atom of aryl

10 group, the carbon atom of alkoxy group and the like can be referred to, and preferably the carbon atom of branched chain-like alkyl group, the carbon atom of alkenyl group and the carbon atom of alkoxy group can

15 be referred to.

The term "optimized structure" means the energy-minimized structure obtained by a usual geometry optimization calculation (Keisan kagaku Njumon, Kodansha, Page 55, 1994) according to a calculation

20 program such as SYBYL (TRIPOS, USA) or the like.

The alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxy carbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonyl-

25 amino, arylsulfonylamino or heterocyclic group in R^1 , R^{1a} , R^{1b} , R^{1c} , R^{1d} , R^{3a} , R^{3b} , R^4 , R^{4a} , R^{4b} , R^5 , R^7 , R^8 , R^9 , R^{10} , R^{15} , R^{16} , R^{24} , R^{24a} , R^{25} and R^{25a} ; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio,

alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group in R^{1f}, R^{3e} and R^{4e}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl- amino or arylsulfonylamino group in R^{0e}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl group in R^{1e}; the alkoxy group in R^{1g} and R^{4g}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group in R³; the alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group in R^{3c} and R^{4c}; the alkyl, alkenyl, cycloalkyl, aryl or aralkyl group in R^{3d}, R^{3f} and R^{4f}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonyl, alkylsulfonylamino or arylsulfonylamino group in R^{4d}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylsulfonyl or heterocyclic group in R¹⁷; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group in R²¹ and R^{21a}; the alkyl, aralkyl or heterocycle-lower alkyl group in R^{21a'}; the alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl,

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between N_1 and N_2 is not less than 5.09 angstroms and not more than 11.67 angstroms, the distance between N_1 and N_3 is not less than 9.47 angstroms and not more than 14.30 angstroms, the distance between N_1 and N_4 is not less than 3.48 angstroms and not more than 12.60 angstroms, the distance between N_1 and N_5 is not less than 8.77 angstroms and not more than 15.67 angstroms, the distance between N_2 and N_3 is not less than 3.78 angstroms and not more than 9.78 angstroms, the distance between N_2 and N_4 is not less than 6.97 angstroms and not more than 13.26 angstroms, the distance between N_2 and N_5 is not less than 9.37 angstroms and not more than 13.32 angstroms, the distance between N_3 and N_4 is not less than 4.83 angstroms and not more than 10.51 angstroms, the distance between N_3 and N_5 is not less than 3.31 angstroms and not more than 9.97 angstroms, and the distance between N_4 and N_5 is not less than 4.32 angstroms and not more than 8.25 angstroms, and more preferred are compounds conforming to a pharmacophore in which N_1 constituting the pharmacophore is a nitrogen atom of unsubstituted or substituted amino, ammonium, amido, thioamido, ureido, isoureido, amidino, guanidino, thioureido, hydrazino or hydrazono group to which one or more hydrogen atoms are bonded, a carbon atom of ethenyl group to which a hydrogen atom is bonded, an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted

or substituted imino group, an oxygen atom of sulfonyl group, an oxygen atom of sulfonyloxy group, an oxygen atom of sulfonic group, an oxygen atom of sulfinyl group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, a sulfur atom of mercapto group, an oxygen atom of hydroxyl group, an oxygen atom of ester, or a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group; N_3 is an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of imino group, an oxygen atom of sulfo group, an oxygen atom of sulfonyl group, an oxygen atom of sulfinyl group, an oxygen atom of sulfonyloxy group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, an oxygen atom of hydroxyl group, an oxygen atom of ester, a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group to which no hydrogen atom is bonded, a nitrogen atom of sulfonamido group or a nitrogen atom of acylsulfonamido group; and each of N_2 , N_4 and N_5 is arbitrary carbon atom constituting a carbon atom of alkyl group, a carbon atom of alkenyl group, a carbon atom of aryl group and a carbon atom of alkoxy group; and further preferred are compounds having an activity on the binding reaction between AP-1 and its recognition sequence.

Among the compounds of general formula [2] of this invention, preferred are those in which AA^3 is L-

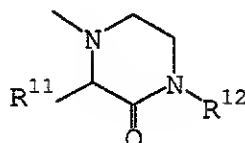
asparagine residue or L-glutamine residue; AA⁴, AA⁶ and AA⁷ are L-leucine residue, L-isoleucine residue, L-alanine residue or L-valine residue; and AA⁵ is L-aspartic acid residue, L-glutamic acid residue, L-serine residue or L-threonine residue.

Among the compounds of general formula [2b] of this invention, preferred are those in which aa³ is L-asparagine residue or L-glutamine residue; aa⁴, aa⁵ and aa⁷ are L-leucine residue, L-isoleucine residue, L-alanine residue or L-valine residue; and aa⁹ is L-aspartic acid residue, L-glutamic acid residue, L-serine residue or L-threonine residue.

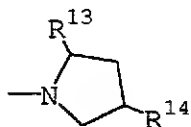
Among the compounds of general formula [3] of this invention, preferred are those in which W is -Z'-COOR^{2'}-, -Z'-CONH-SO₂R^{28'}-, -CONH-CH₂COOR^{2'}- or -CONH-CH₂CH₂COOR^{2'}- (in these formulas, Z' represents -(CH₂)_{n'}-, in which n' is 0, 1 or 2 or -CH=CH-, R^{28'} represents unsubstituted or substituted alkyl group, R^{2'} represents hydrogen atom or a protecting group for carboxyl group, and X¹ represents -C(O)-, -CH(OH)- or -CH₂-; more preferred are those in which R¹ is unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group, R³ is unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group, and R⁴ is unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group; further preferred are those in which R³ is alkoxy group, hydroxyl group or alkylcarbonyloxy group, and X¹ is -

C(O)-; and yet further preferred are those in which R¹ is alkoxy group and R⁴ is alkoxy group.

Among the compounds of general formula [4] of this invention, preferred are those in which R⁵ is
 5 alkoxy group or acylamino group, and ring A is a group represented by the following formula:

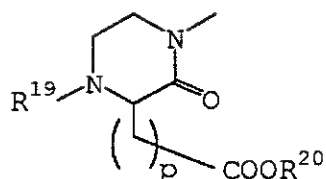


wherein R¹¹ is alkyl or alkoxy carbonyl group and R¹² is alkyl group, or a group represented by the following formula:



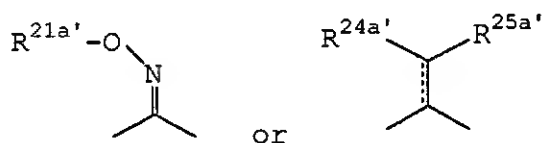
10 wherein R¹³ is alkyl or alkoxy carbonyl group and R¹⁴ is alkoxy or alkanoyloxy group.

Among the compounds of general formula [5] of this invention, preferred are those in which R¹⁵ and R¹⁶ are the same or different and represent alkoxy group,
 15 and ring B represents the following formula:



wherein R^{19} represents acyl group, and R^{20} represents a protecting group for carboxyl group and p represents 0, 1 or 2.

Among the compounds of general formula [a] of this invention, preferred are those in which R^{1a} is unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group, R^{3a} and R^{4a} are the same or different and represent unprotected or protected hydroxyl group or unsubstituted or substituted alkoxy group, X^{1a} represents $-C(O)-$, $-CH(OH)-$, $-CH_2-$ or the following formulas:



wherein $R^{21a'}$ represents unsubstituted or substituted alkyl, aralkyl or heterocycle-lower alkyl group, $R^{24a'}$ and $R^{25a'}$ are the same or different and represent hydrogen atom, unprotected or protected carboxyl group or unsubstituted or substituted alkyl, alkoxycarbonyl, aryloxy carbonyl or carbamoyl group, W^a represents $-Z^{a'}-$, $-COR^{26a'}$, $-Z^{a'}-COOR^{2a'}$, $-O-CH_2COOR^{2a'}$, $-O-CH_2CH_2COOR^{2a'}$, $-CONH-CH_2COOR^{2a'}$ or $-CONH-CH_2CH_2COOR^{2a'}$ (in these formulas, $Z^{a'}$

represents $-(CH_2)_{n^{a'}}$ wherein $n^{a'}$ is 0, 1, 2 or 3,
 $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$, $R^{2a'}$ represents
hydrogen atom or a protecting group for carboxyl group,
and $R^{26a'}$ represents $-NHSO_2R^{28a'}$ wherein $R^{28a'}$ is
5 unsubstituted or substituted alkyl group.

Among the compounds of general formula [b] of
this invention, preferred are those in which R^{1b}
represents unsubstituted or substituted alkoxy group,
 R^{3b} and R^{4b} are the same or different and represent
10 unprotected or protected hydroxyl group or
unsubstituted or substituted alkoxy group, X^{1b} is $-C(O)-$
, and Z^b is $-(CH_2)_2-$.

Among the compounds of general formula [c] of
this invention, preferred are those in which R^{1c}
15 represents unsubstituted or substituted alkoxy group;
 R^{2c} represents hydrogen atom or a protecting group for
carboxyl group; R^{3c} and R^{4c} may be the same or different
and represent unsubstituted or substituted alkoxy
group; X^{1c} is $-C(O)-$; and Z^c is $-(CH_2)_2-$.

20 Among the compounds of general formula [d] of
this invention, preferred are those in which R^{1d} is
unsubstituted or substituted alkoxy group; R^{3d} is
unsubstituted or substituted alkyl group; R^{4d} is
unsubstituted or substituted acyl group; X^{1d} is $-C(O)-$;
25 and Z^d is $-(CH_2)_2-$.

Among the compounds of general formula [e] of
this invention, preferred are those in which R^{0e} is
hydrogen atom or halogen atom; R^{1e} is unsubstituted or

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substituted alkyl group; R^{3e} and R^{4e} independently represent unsubstituted or substituted alkoxy group; X^{1e} is $-C(O)-$; and Z^e is a bonding unit.

Among the compounds of general formula [f] of this invention, preferred are those in which R^{1f} is unsubstituted or substituted alkoxy group; R^{3f} and R^{4f} independently represent unsubstituted or substituted alkyl group; X^{1f} is $-C(O)-$; and Z^f is $-CH_2-$.

As typical compounds of this invention, the following compounds can be referred to, for example, provided that Ac represents an acetyl group.

- Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Leu-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth L-cysteine residues)
- 15 • Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Leu-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Gly-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth L-cysteine residues)
- 20 • Ac-Cys-Gly-Gln-Leu-Asp-Leu-Ala-Asn-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth L-cysteine residues)
- Ac-Cys-Gly-Gln-Leu-Ser-Leu-Ala-Asp-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth cysteine residues)
- 25 • Ac-Cys-Gly-Asn-Leu-Asp-Leu-Ala-Asp-Gly-Cys-NH₂
(having a disulfide linkage between the first and tenth

• Ac-Asn-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys-NH₂
(having a disulfide linkage between the second and
eleventh L-cysteine residues)

- 5 • Ac-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys-NH₂
(having a disulfide linkage between the first and tenth
L-cysteine residues)
- Ac-Asn-Cys-Gly-Asn-Ala-Leu-Ala-Leu-Gly-Ser-Cys-NH₂
(having a disulfide linkage between the second and
10 eleventh L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Asp-Cys-NH₂
(having a disulfide linkage between the first and tenth
L-cysteine residues)
- Ac-Cys-Gly-Asn-Leu-Leu-Ser-Leu-Gly-Asp-Cys-NH₂
15 (having a disulfide linkage between the first and tenth
L-cysteine residues)
- (3S)-8-(3-methylbutylidene)-4-(4-methylpentanoyl)-
1-thia-4-azaspiro[4.5]-deecane-3-carboxylic acid
- 2-[(2S)-4-(2,4-diisobutoxybenzoyl)-1-(3-
20 methylbutanoyl)-3-oxohexahydro-2-pyrazinyl]-acetic acid
- 2-(2-isobutoxy-5-{[(2S,4R)-4-(isobutyryloxy)-2-
(isopropoxycarbonyl)tetrahydro-1H-1-pyrrolyl]carbonyl}-
phenyl)-acetic acid
- 2-(2-isobutoxy-5-{[(2S)-4-isopentyl-2-
25 (isopropoxycarbonyl)-3-oxohexahydro-1-
pyrazinyl]carbonyl}-phenyl)-acetic acid
- 2-(5-{[(2R)-2,4-diisopentyl-3-oxohexahydro-1-
pyrazinyl]-carbonyl}-2-isobutoxyphenyl)-acetic acid

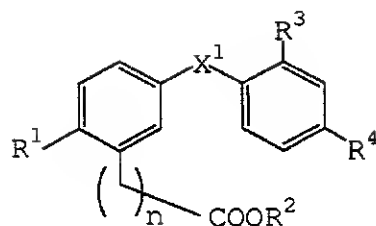
Further, the compounds of the following
Tables 1 to 37 can also be referred to.

In the tables, meanings of the abbreviations
are as follows:

- 5 Me: CH_3 ; Et: C_2H_5 ; nPr: $\text{CH}_2\text{CH}_2\text{CH}_3$; iPr: $\text{CH}(\text{CH}_3)_2$;
 iBu: $\text{CH}_2\text{CH}(\text{CH}_3)_2$; iAm: $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$; Ph: phenyl;
 Py: pyridyl

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[Table 1]



n	X ¹	R ¹	R ²	R ³	R ⁴
0	C(O)	O-iBu	H	CN	CN
0	C(O)	O-iBu	H	NO ₂	NO ₂
0	C(O)	O-iBu	H	COOCH ₃	COOCH ₃
0	C(O)	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅
0	C(O)	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	H	O-iBu	O-iBu
0	C(O)	O-iBu	CH ₂ CH ₃	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₂ CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	CH ₂ CH ₃	O-iBu	O-iBu
0	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
2	C(O)	S-iBu	H	S-iBu	S-iBu
2	C(O)	NH-iBu	H	NH-iBu	NH-iBu
0	C(O)	SCH ₃	H	SCH ₃	SCH ₃
0	C(O)	CH ₂ COOH	H	CH ₂ COOH	CH ₂ COOH
0	C(O)	CH ₃	H	CH ₃	CH ₃
1	C(O)	CH ₃	H	CH ₃	CH ₃
0	C(O)	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅
0	C(O)	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁

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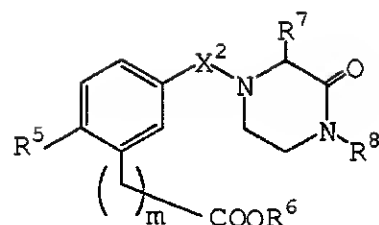
n	X ¹	R ¹	R ²	R ³	R ⁴
0	C(O)	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅
0	C(O)	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
0	C(O)	OCH ₃	H	OCH ₃	OCH ₃
0	C(O)	OC ₆ H ₅	H	OC ₆ H ₅	OC ₆ H ₅
0	C(O)	O-iBu	H	COCH ₃	COCH ₃
0	C(O)	O-iBu	H	COOC ₂ H ₅	COOC ₂ H ₅
0	C(O)	O-iBu	H	COOC ₆ H ₅	COOC ₆ H ₅
0	C(O)	O-iBu	H	CONH ₂	CONH ₂
0	C(O)	O-iBu	H	S(O)CH ₃	S(O)CH ₃
0	C(O)	O-iBu	H	S(O) ₂ CH ₃	S(O) ₂ CH ₃
0	C(O)	NH ₂	H	NH ₂	NH ₂
0	C(O)	2-Py	H	2-Py	2-Py
0	CH(OH)	O-iBu	H	CN	CN
0	CH(OH)	O-iBu	H	NO ₂	NO ₂
0	CH(OH)	O-iBu	H	COOCH ₃	COOCH ₃
0	CH(OH)	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅
0	CH(OH)	O-iBu	H	O-iBu	O-iBu
1	CH(OH)	O-iBu	H	O-iBu	O-iBu
2	CH(OH)	O-iBu	H	O-iBu	O-iBu
0	CH(OH)	O-iBu	CH ₃	O-iBu	O-iBu
1	CH(OH)	O-iBu	CH ₃	O-iBu	O-iBu
2	CH(OH)	O-iBu	CH ₃	O-iBu	O-iBu
0	CH(OH)	SCH ₃	H	SCH ₃	SCH ₃
0	CH(OH)	CH ₂ COOH	H	CH ₂ COOH	CH ₂ COOH
0	CH(OH)	CH ₃	H	CH ₃	CH ₃
1	CH(OH)	CH ₃	H	CH ₃	CH ₃
0	CH(OH)	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅
0	CH(OH)	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁
0	CH(OH)	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅

n	X ¹	R ¹	R ²	R ³	R ⁴
0	CH(OH)	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
0	CH(OH)	OCH ₃	H	OCH ₃	OCH ₃
0	CH(OH)	OC ₆ H ₅	H	OC ₆ H ₅	OC ₆ H ₅
0	CH(OH)	O-iBu	H	COCH ₃	COCH ₃
0	CH(OH)	O-iBu	H	COOC ₂ H ₅	COOC ₂ H ₅
0	CH(OH)	O-iBu	H	COOC ₆ H ₅	COOC ₆ H ₅
0	CH(OH)	O-iBu	H	CONH ₂	CONH ₂
0	CH(OH)	O-iBu	H	S(O)CH ₃	S(O)CH ₃
0	CH(OH)	O-iBu	H	S(O) ₂ CH ₃	S(O) ₂ CH ₃
0	CH(OH)	NH ₂	H	NH ₂	NH ₂
0	CH(OH)	2-Py	H	2-Py	2-Py
0	CH ₂	O-iBu	H	CN	CN
0	CH ₂	O-iBu	H	NO ₂	NO ₂
0	CH ₂	O-iBu	H	COOCH ₃	COOCH ₃
0	CH ₂	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅
0	CH ₂	O-iBu	H	O-iBu	O-iBu
1	CH ₂	O-iBu	H	O-iBu	O-iBu
2	CH ₂	O-iBu	H	O-iBu	O-iBu
0	CH ₂	O-iBu	CH ₃	O-iBu	O-iBu
1	CH ₂	O-iBu	CH ₃	O-iBu	O-iBu
2	CH ₂	O-iBu	CH ₃	O-iBu	O-iBu
0	CH ₂	CH ₂ COOH	H	CH ₂ COOH	CH ₂ COOH
0	CH ₂	CH ₃	H	CH ₃	CH ₃
1	CH ₂	CH ₃	H	CH ₃	CH ₃
0	CH ₂	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅
0	CH ₂	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁
0	CH ₂	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅
0	CH ₂	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
0	CH ₂	OCH ₃	H	OCH ₃	OCH ₃

n	X ¹	R ¹	R ²	R ³	R ⁴
0	CH ₂	OC ₆ H ₅	H	OC ₆ H ₅	OC ₆ H ₅
0	CH ₂	O-iBu	H	COCH ₃	COCH ₃
0	CH ₂	O-iBu	H	COOC ₂ H ₅	COOC ₂ H ₅
0	CH ₂	O-iBu	H	COOC ₆ H ₅	COOC ₆ H ₅
0	CH ₂	O-iBu	H	CONH ₂	CONH ₂
0	CH ₂	SCH ₃	H	SCH ₃	SCH ₃
0	CH ₂	O-iBu	H	S(O)CH ₃	S(O)CH ₃
0	CH ₂	O-iBu	H	S(O) ₂ CH ₃	S(O) ₂ CH ₃
0	CH ₂	NH ₂	H	NH ₂	NH ₂
0	CH ₂	2-Py	H	2-Py	2-Py
0	CH ₂	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
1	CH ₂	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
2	CH ₂	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
0	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
1	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
2	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
0	CH(OH)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
1	CH(OH)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
2	CH(OH)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
0	CH ₂	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
1	CH ₂	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	CH ₂	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
0	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
1	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
0	CH(OH)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
1	CH(OH)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	CH(OH)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr

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[Table 2]

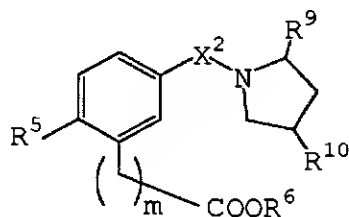


m	X ²	R ⁵	R ⁶	R ⁷	R ⁸
1	C(O)	O-iBu	H	n-Bu	iAm
0	C(O)	H	CH ₃	H	H
0	C(O)	Cl	H	Cl	C(O)CH ₃
1	C(O)	CN	H	CN	C(O)CH(CH ₃) ₂
1	C(O)	NO ₂	H	NO ₂	C(O)-iBu
1	C(O)	COOCH ₃	H	COOCH ₃	COOCH ₃
1	C(O)	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅
1	C(O)	O-iBu	H	iAm	iAm
1	C(O)	O-iBu	H	C(O)OCH(CH ₃) ₂	iAm
2	C(O)	O-iBu	H	iAm	iAm
1	C(O)	NHC(O)-iBu	H	iAm	iAm
1	C(O)	NHC(O)-iBu	H	C(O)OCH(CH ₃) ₂	iAm
2	C(O)	NHC(O)-iBu	H	iAm	iAm
1	C(O)	NHC(O)-iPr	H	iAm	iAm
1	C(O)	NHC(O)-iPr	H	C(O)OCH(CH ₃) ₂	iAm
2	C(O)	NHC(O)-iPr	H	iAm	iAm
1	C(O)	O-iAm	CH ₃	iAm	O-iAm
1	C(O)	CH ₂ COOH	H	CH ₂ COOH	CH ₂ COOH
0	C(O)	CH ₃	H	CH ₃	CH ₃
1	C(O)	CH ₃	H	CH ₃	CH ₃
1	C(O)	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅

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m	X ²	R ⁵	R ⁶	R ⁷	R ⁸
1	C(O)	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁
1	C(O)	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅
1	C(O)	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
1	C(O)	OCH ₃	H	OCH ₃	OCH ₃
1	C(O)	OC ₆ H ₅	H	OC ₆ H ₅	OC ₆ H ₅
1	C(O)	COCH ₃	H	COCH ₃	COCH ₃
1	C(O)	COOC ₂ H ₅	H	COOC ₂ H ₅	COOC ₂ H ₅
1	C(O)	COOC ₆ H ₅	H	COOC ₆ H ₅	COOC ₆ H ₅
1	C(O)	CONH ₂	H	CONH ₂	CONH ₂
1	C(O)	SCH ₃	H	SCH ₃	SCH ₃
1	C(O)	S(O)CH ₃	H	S(O)CH ₃	S(O)CH ₃
1	C(O)	S(O) ₂ CH ₃	H	S(O) ₂ CH ₃	S(O) ₂ CH ₃
1	C(O)	NH ₂	H	NH ₂	NH ₂
2	C(O)	2-Py	H	2-Py	2-Py

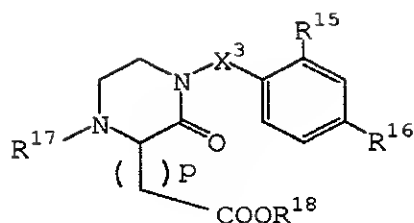
[Table 3]



m	X ²	R ⁵	R ⁶	R ⁹	R ¹⁰
1	C(O)	O-iBu	H	CH ₂ CH ₂ -iBu	O-iBu
0	C(O)	Cl	CH ₃	Cl	Cl
0	C(O)	CN	CH ₃	CN	CN
0	C(O)	NO ₂	H	NO ₂	NO ₂
0	C(O)	COOCH ₃	H	COOCH ₃	COOCH ₃
0	C(O)	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅

m	X ²	R ⁵	R ⁶	R ⁹	R ¹⁰
0	C(O)	O-iBu	H	COO-iBu	O-iBu
1	C(O)	O-iBu	H	COO-iBu	O-iBu
2	C(O)	O-iBu	H	COO-iBu	-O-iBu
0	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
1	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
2	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
0	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
1	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
0	C(O)	O-iAm	H	O-iAm	O-iAm
1	C(O)	CH ₂ COOH	H	CH ₂ COOH	CH ₂ COOH
0	C(O)	CH ₃	H	CH ₃	CH ₃
1	C(O)	CH ₃	H	CH ₃	CH ₃
1	C(O)	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅
1	C(O)	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁
1	C(O)	C ₆ H ₅	H	C ₆ H ₅	C ₆ H ₅
1	C(O)	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
1	C(O)	OCH ₃	H	OCH ₃	OCH ₃
1	C(O)	OC ₆ H ₅	H	OC ₆ H ₅	OC ₆ H ₅
1	C(O)	COCH ₃	H	COCH ₃	COCH ₃
1	C(O)	COOC ₂ H ₅	H	COOC ₂ H ₅	COOC ₂ H ₅
1	C(O)	COOC ₆ H ₅	H	COOC ₆ H ₅	COOC ₆ H ₅
1	C(O)	CONH ₂	H	CONH ₂	CONH ₂
1	C(O)	SCH ₃	H	SCH ₃	SCH ₃
1	C(O)	S(O)CH ₃	H	S(O)CH ₃	S(O)CH ₃
1	C(O)	S(O) ₂ CH ₃	H	S(O) ₂ CH ₃	S(O) ₂ CH ₃
1	C(O)	NH ₂	H	NH ₂	NH ₂
1	C(O)	2-Py	H	2-Py	2-Py

[Table 4]

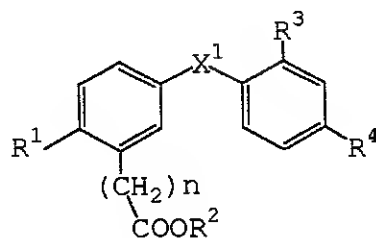


n	X ³	R ¹⁵	R ¹⁶	R ¹⁷	R ¹⁸
1	C(O)	Cl	Cl	C(O)CH ₃	CH ₃
1	C(O)	CN	CN	C(O)CH(CH ₃) ₂	CH ₃
1	C(O)	NO ₂	NO ₂	C(O)-iBu	H
1	C(O)	COOCH ₃	COOCH ₃	COOCH ₃	H
0	C(O)	O-iBu	O-iBu	C(O)CH(CH ₃) ₂	H
1	C(O)	O-iBu	O-iBu	C(O)CH(CH ₃) ₂	H
2	C(O)	O-iBu	O-iBu	C(O)CH(CH ₃) ₂	H
1	C(O)	O-iBu	O-iBu	C(O)-iBu	H
1	C(O)	O-iBu	O-iBu	C(O)CH ₂ -iBu	H
1	C(O)	O-iBu	O-iBu	iBu	H
1	C(O)	O-iBu	O-iBu	iAm	H
1	C(O)	O-iBu	O-iBu	CH ₂ CH ₂ -iBu	H
1	C(O)	NHC(O)-iBu	NHC(O)-iBu	iBu	H
1	C(O)	NHC(O)-iBu	NHC(O)-iBu	iAm	H
1	C(O)	NHC(O)-iBu	NHC(O)-iBu	CH ₂ CH ₂ -iBu	H
1	C(O)	NHC(O)-iPr	NHC(O)-iPr	iBu	H
1	C(O)	NHC(O)-iPr	NHC(O)-iPr	iAm	H
1	C(O)	NHC(O)-iPr	NHC(O)-iPr	CH ₂ CH ₂ -iBu	H
1	C(O)	CH ₂ COOH	CH ₂ COOH	CH ₂ COOH	H
1	C(O)	CH ₃	CH ₃	CH ₃	H
1	C(O)	CHCHC ₆ H ₅	CHCHC ₆ H ₅	CHCHC ₆ H ₅	H

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X^1	R^1	R^2	R^3	R^4
C(O)	C_6H_5	H	C_6H_5	C_6H_5
C(O)	$CH_2C_6H_5$	H	$CH_2C_6H_5$	$CH_2C_6H_5$
C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
C(O)	NHC(O)-iPr	H	O-iBu	O-iBu
C(O)	O-iBu	H	NHC(O)-iPr	O-iBu
C(O)	O-iBu	H	O-iBu	NHC(O)-iPr
C(O)	O-iBu	H	NHC(O)-iPr	NHC(O)-iPr
C(O)	C(O)CH ₂ CH(CH ₃) ₂	H	C(O)CH ₂ CH(CH ₃) ₂	C(O)CH ₂ CH(CH ₃) ₂
C(O)	C(O)CH ₂ CH(CH ₃) ₂	H	O-iBu	O-iBu
C(O)	O-iBu	H	C(O)CH ₂ CH(CH ₃) ₂	C(O)CH ₂ CH(CH ₃) ₂
C(O)	CH ₂ CH ₂ CH(CH ₃) ₂	H	CH ₂ CH ₂ CH(CH ₃) ₂	CH ₂ CH ₂ CH(CH ₃) ₂
C(O)	CH ₂ CH ₂ CH(CH ₃) ₂	H	O-iBu	O-iBu
C(O)	O-iBu	H	CH ₂ CH ₂ CH(CH ₃) ₂	CH ₂ CH ₂ CH(CH ₃) ₂
C(O)	C(O)NH-iPr	H	O-iBu	O-iBu
C(O)	O-iBu	H	C(O)NH-iPr	C(O)NH-iPr
CH(OH)	O-iBu	H	O-iBu	O-iBu
CH ₂	O-iBu	H	O-iBu	O-iBu

[Table 6]



n	X^1	R^1	R^2	R^3	R^4
3	C(O)	O-iBu	H	O-iBu	O-iBu
0	C(O)	O-iAm	H	O-iAm	O-iAm
1	C(O)	O-iAm	CH ₃	O-iAm	O-iAm

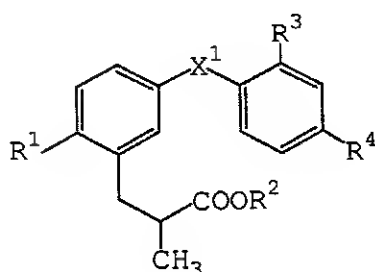
n	X ¹	R ¹	R ²	R ³	R ⁴
1	C(O)	O-iAm	H	O-iAm	O-iAm
2	C(O)	O-iAm	H	O-iAm	O-iAm
3	C(O)	O-iAm	H	O-iAm	O-iAm
2	C(O)	O-iAm	H	O-iBu	O-iBu
2	C(O)	O-iAm	H	O-iBu	O-iAm
2	C(O)	O-iBu	H	OH	O-iBu
2	C(O)	O-iBu	H	OH	O-iAm
2	C(O)	S-iBu	H	OH	S-iBu
2	C(O)	NH-iBu	H	OH	NH-iBu
2	C(O)	OH	H	O-iBu	O-iBu
2	C(O)	O-iBu	H	H	O-iBu
2	C(O)	O-iBu	H	OCH ₃	O-iBu

[Table 7]

n	X ¹	R ¹	R ²	R ³	R ⁴
2	C(O)	O-iBu	H	F	O-iBu
2	C(O)	O-iBu	H	OCO-iPr	O-iBu
2	C(O)	O-iBu	H	O(CH ₂) ₃ COOH	O-iBu
2	C(O)	O-iBu	H	O(CH ₂) ₅ CONH ₂	O-iBu
2	C=N-OH	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
2	C=N-OH	O-iBu	H	OH	O-iBu
2	C=N-OCH ₂ CONH ₂	O-iBu	H	OH	O-iBu

n	X ¹	R ¹	R ²	R ³	R ⁴
2	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	OH	O-iBu
2	CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
2	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
2	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
2	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
2	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
2	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
2	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

[Table 8]



X ¹	R ¹	R ²	R ³	R ⁴
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
C(O)	O-iAm	H	O-iAm	O-iAm
C(O)	O-iBu	H	O-iAm	O-iBu
C(O)	O-iBu	H	O-iAm	O-iAm
C(O)	O-iBu	H	OH	O-iBu
C(O)	O-iBu	H	OH	O-iAm
C(O)	OH	H	O-iBu	O-iBu
C(O)	O-iBu	H	OCH ₃	O-iBu
C(O)	O-iBu	H	F	O-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu

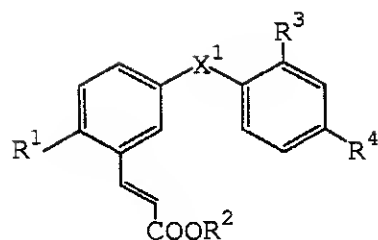
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X^1	R^1	R^2	R^3	R^4
C(O)	O-iBu	H	O(CH ₂) ₃ COOH	O-iBu
C(O)	O-iBu	H	O(CH ₂) ₅ CONH ₂	O-iBu

[Table 9]

X^1	R^1	R^2	R^3	R^4
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

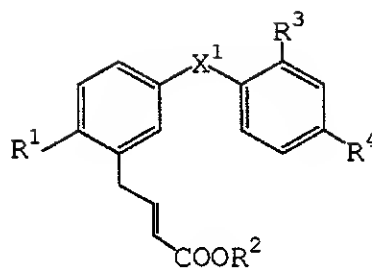
[Table 10]



X^1	R^1	R^2	R^3	R^4
C(O)	O-iBu	H	OH	O-iBu
C(O)	OH	H	O-iBu	O-iBu
C(O)	O-iBu	H	OCH ₃	O-iBu
C(O)	O-iBu	H	F	O-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu
C(O)	O-iBu	H	O(CH ₂) ₃ COOH	O-iBu
C(O)	O-iBu	H	O(CH ₂) ₅ CONH ₂	O-iBu
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

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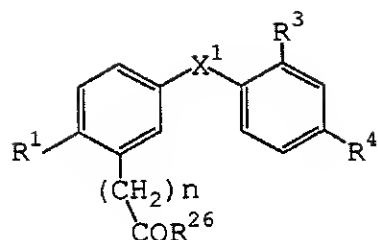
[Table 11]



X ¹	R ¹	R ²	R ³	R ⁴
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
C(O)	O-iBu	H	OH	O-iBu
C(O)	OH	H	O-iBu	O-iBu
C(O)	O-iBu	H	OCH ₃	O-iBu
C(O)	O-iBu	H	F	O-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu
C(O)	O-iBu	H	O(CH ₂) ₃ COOH	O-iBu
C(O)	O-iBu	H	O(CH ₂) ₅ CONH ₂	O-iBu
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

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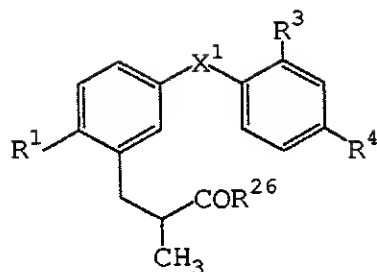
[Table 12]



n	X ¹	R ¹	R ²⁶	R ³	R ⁴
2	C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	NHSO ₂ CH ₃	OH	O-iBu
2	C(O)	OH	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	NHSO ₂ CH ₃	OCH ₃	O-iBu
2	C(O)	O-iBu	NHSO ₂ CH ₃	F	O-iBu
2	C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
2	C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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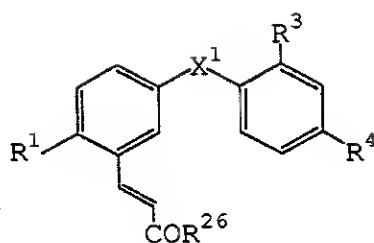
[Table 13]



X^1	R^1	R^{26}	R^3	R^4
C(O)	O-iBu	NHSO ₂ CH ₃	OH	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCH ₃	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	F	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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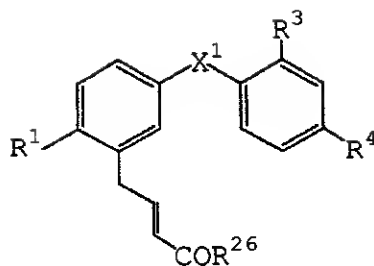
[Table 14]



X^1	R^1	R^{26}	R^3	R^4
C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OH	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCH ₃	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	F	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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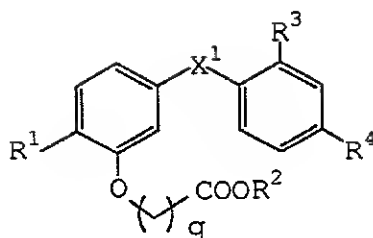
[Table 15]



X ¹	R ¹	R ²⁶	R ³	R ⁴
CH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OH	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCH ₃	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	F	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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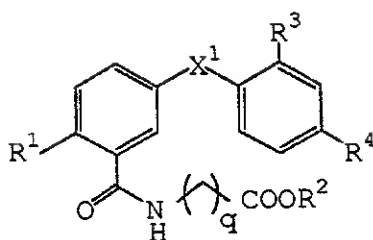
[Table 16]



q	X ¹	R ¹	R ²	R ³	R ⁴
1	C(O)	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
1	C(O)	O-iBu	H	OH	O-iBu
1	C(O)	OH	H	O-iBu	O-iBu
1	C(O)	O-iBu	H	OCH ₃	O-iBu
1	C(O)	O-iBu	H	F	O-iBu
1	C(O)	O-iBu	H	OCO-iPr	O-iBu
1	C=N-OH	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
1	CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

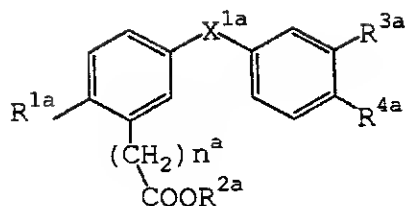
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[Table 17]



q	X ¹	R ¹	R ²	R ³	R ⁴
1	C(O)	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
1	C(O)	O-iBu	H	OH	O-iBu
1	C(O)	OH	H	O-iBu	O-iBu
1	C(O)	O-iBu	H	OCH ₃	O-iBu
1	C(O)	O-iBu	H	F	O-iBu
1	C(O)	O-iBu	H	OCO-iPr	O-iBu
1	C=N-OH	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
1	CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

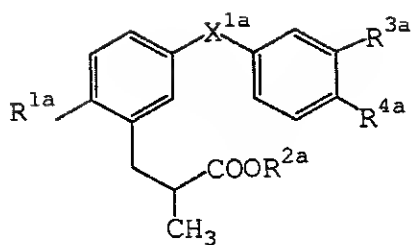
[Table 18]



n	X^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}
1	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	H	O-iBu	O-iBu
2	CH(OH)	O-iBu	H	O-iBu	O-iBu
2	CH ₂	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	H	OCO-iPr	O-iBu
2	C=N-OH	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
2	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
2	CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
2	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
2	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
2	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
2	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
2	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
2	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

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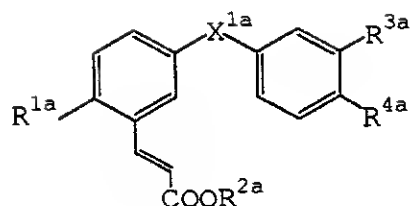
[Table 19]



X^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	H	O-iBu	O-iBu
CH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

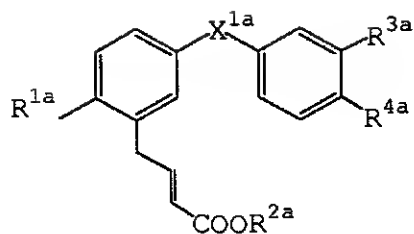
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[Table 20]



X^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	H	O-iBu	O-iBu
CH ₂	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

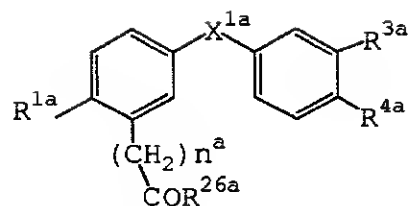
[Table 21]



X^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	H	O-iBu	O-iBu
CH ₂	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu
C=N-OH	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
C=CH-COOH	O-iBu	H	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

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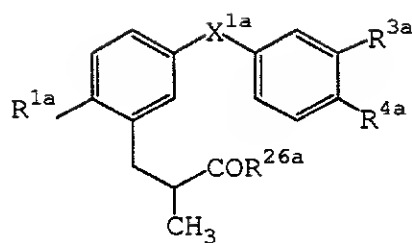
[Table 22]



n^a	X^{1a}	R^{1a}	R^{2a}	R^{3a}	R^{4a}
2	C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
2	C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
2	CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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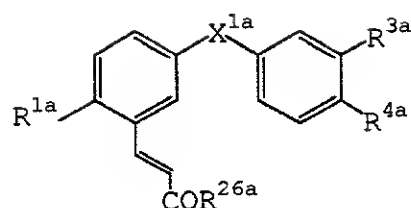
[Table 23]



X^{1a}	R^{1a}	R^{26a}	R^{3a}	R^{4a}
C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

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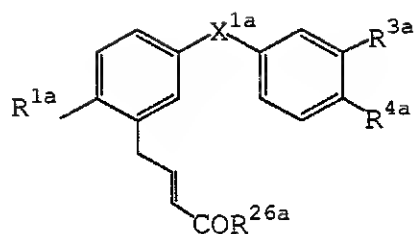
[Table 24]



X^{1a}	R^{1a}	R^{26a}	R^{3a}	R^{4a}
C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

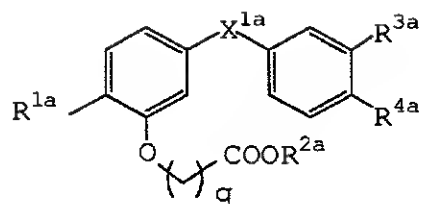
T02050" 550E350

[Table 25]



X^{1a}	R^{1a}	R^{26a}	R^{3a}	R^{4a}
C(O)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C(O)	O-iBu	NHSO ₂ CH ₃	OCO-iPr	O-iBu
C=N-OH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CH ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ C ₆ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=N-OCH ₂ -3-Py	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHSO ₂ CH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCOCH ₃	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHNHCONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
C=CH-COOC ₂ H ₅	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ COOH	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu
CHCH ₂ CONH ₂	O-iBu	NHSO ₂ CH ₃	O-iBu	O-iBu

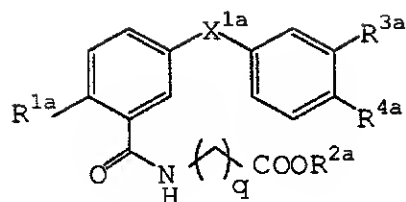
[Table 26]



q	X ^{1a}	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}
1	C(O)	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
1	CH(OH)	O-iBu	H	O-iBu	O-iBu
1	CH ₂	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	H	OCO-iPr	O-iBu
1	C=N-OH	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
1	CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

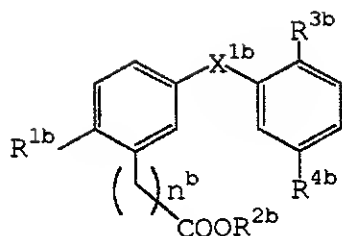
T04050" 6550E860

[Table 27]

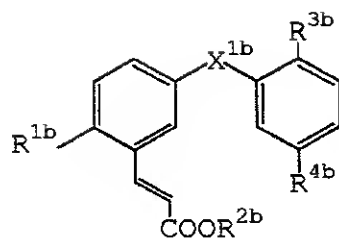


q	X ^{1a}	R ^{1a}	R ^{2a}	R ^{3a}	R ^{4a}
1	C(O)	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	CH ₃	O-iBu	O-iBu
2	C(O)	O-iBu	H	O-iBu	O-iBu
1	CH(OH)	O-iBu	H	O-iBu	O-iBu
1	CH ₂	O-iBu	H	O-iBu	O-iBu
1	C(O)	O-iBu	H	OCO-iPr	O-iBu
1	C=N-OH	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CH ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ C ₆ H ₅	O-iBu	H	O-iBu	O-iBu
1	C=N-OCH ₂ -3-Py	O-iBu	H	O-iBu	O-iBu
1	CHNH ₂ SO ₂ CH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCOCH ₃	O-iBu	H	O-iBu	O-iBu
1	CHNHCONH ₂	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOH	O-iBu	H	O-iBu	O-iBu
1	C=CH-COOC ₂ H ₅	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ COOH	O-iBu	H	O-iBu	O-iBu
1	CHCH ₂ CONH ₂	O-iBu	H	O-iBu	O-iBu

n ^b	X ^{1b}	R ^{1b}	R ^{2b}	R ^{3b}	R ^{4b}
0	C(O)	OCH ₂ C ₆ H ₅	H	OCH ₂ C ₆ H ₅	OCH ₂ C ₆ H ₅
1	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	CH ₂ CH ₃	O-iBu	O-iBu
1	C(O)	CHCHC ₆ H ₅	H	CHCHC ₆ H ₅	CHCHC ₆ H ₅
1	C(O)	C ₆ H ₁₁	H	C ₆ H ₁₁	C ₆ H ₁₁
1	C(O)	CH ₂ C ₆ H ₅	H	CH ₂ C ₆ H ₅	CH ₂ C ₆ H ₅
1	C(O)	O-iBu	H	COOC ₂ H ₅	COOC ₂ H ₅
2	CH(OH)	O-iBu	H	O-iBu	O-iBu
2	CH ₂	O-iBu	H	O-iBu	O-iBu
2	CH ₂	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	CH(OH)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
2	C(O)	O-iBu	H	OCO-iPr	O-iBu

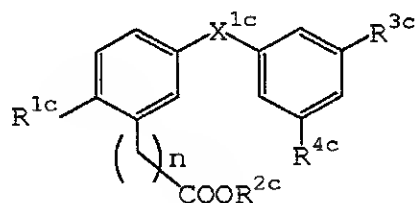


[Table 29]



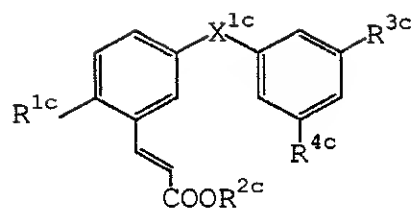
X^{1b}	R^{1b}	R^{2b}	R^{3b}	R^{4b}
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
CH(OH)	O-iBu	H	O-iBu	O-iBu
CH ₂	O-iBu	CH ₃	O-iBu	O-iBu
C(O)	NHC(O)-iPr	H	NHC(O)-iPr	NHC(O)-iPr
C(O)	O-iBu	H	OCO-iPr	O-iBu

[Table 30]



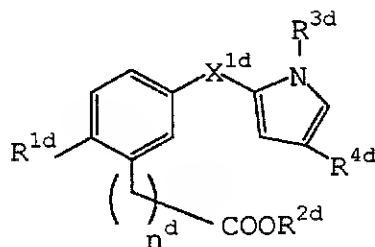
n	X^{1c}	R^{1c}	R^{2c}	R^{3c}	R^{4c}
1	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	H	O-iBu	O-iBu
2	C(O)	O-iBu	CH ₂ CH ₃	O-iBu	O-iBu
2	CH ₂	O-iBu	H	O-iBu	O-iBu
2	C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
2	C(O)	O-iBu	H	OCO-iPr	O-iBu

[Table 31]



X ^{1c}	R ^{1c}	R ^{2c}	R ^{3c}	R ^{4c}
C(O)	O-iBu	H	O-iBu	O-iBu
C(O)	O-iBu	CH ₃	O-iBu	O-iBu
CH ₂	O-iBu	H	O-iBu	O-iBu
C(O)	NHC(O)-iBu	H	NHC(O)-iBu	NHC(O)-iBu
C(O)	O-iBu	H	OCO-iPr	O-iBu

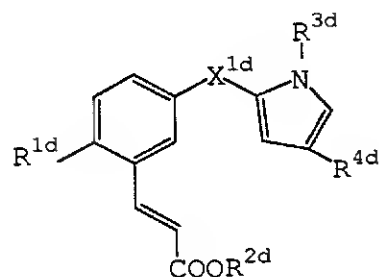
[Table 32]



n ^d	X ^{1d}	R ^{1d}	R ^{2d}	R ^{3d}	R ^{4d}
1	C(O)	C ₆ H ₁₁	H	iAm	CO-iBu
1	C(O)	C ₆ H ₅	H	iAm	CO-iBu
1	C(O)	CH ₂ C ₆ H ₅	H	iAm	CO-iBu
1	C(O)	OC ₆ H ₅	H	iAm	CO-iBu
1	C(O)	S-iBu	H	iAm	CO-iBu
1	C(O)	2-Py	H	iAm	CO-iBu

n^d	X^{1d}	R^{1d}	R^{2d}	R^{3d}	R^{4d}
1	C(O)	CO-iBu	H	C_6H_{11}	CO-iBu
1	C(O)	CO-iBu	H	C_6H_5	CO-iBu
1	C(O)	CO-iBu	H	$CH_2C_6H_5$	CO-iBu
1	C(O)	CO-iBu	H	iAm	$CH_2C_6H_5$
1	C(O)	CO-iBu	H	iAm	C_6H_{11}
1	C(O)	CO-iBu	H	iAm	$NHSO_2C_6H_5$
2	C(O)	O-iAm	H	iAm	CO-iBu
2	CH(OH)	CO-iBu	H	iAm	CO-iBu
2	CH_2	CO-iBu	H	iAm	CO-iBu
2	C(O)	O-iAm	CH_3	iAm	CO-iBu

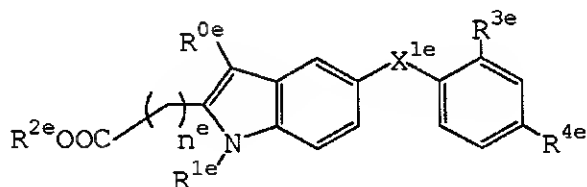
[Table 33]



X^{1d}	R^{1d}	R^{2d}	R^{3d}	R^{4d}
C(O)	$CH_2C_6H_5$	H	iAm	CO-iBu
C(O)	C_6H_{11}	H	iAm	CO-iBu
C(O)	C_6H_5	H	iAm	CO-iBu
C(O)	OC_6H_5	H	iAm	CO-iBu
C(O)	S-iBu	H	iAm	CO-iBu
C(O)	$NHSO_2C_6H_5$	H	iAm	CO-iBu
C(O)	2-Py	H	iAm	CO-iBu
C(O)	CO-iBu	H	C_6H_{11}	CO-iBu
C(O)	CO-iBu	H	C_6H_5	CO-iBu
C(O)	CO-iBu	H	$CH_2C_6H_5$	CO-iBu

X^{1d}	R^{1d}	R^{2d}	R^{3d}	R^{4d}
C(O)	CO-iBu	H	iAm	CH ₂ C ₆ H ₅
C(O)	CO-iBu	H	iAm	C ₆ H ₁₁
C(O)	CO-iBu	H	iAm	C ₆ H ₅
C(O)	CO-iBu	H	iAm	NHSO ₂ C ₆ H ₅
CH(OH)	CO-iBu	H	iAm	CO-iBu
CH ₂	CO-iBu	H	iAm	CO-iBu
C(O)	CO-iBu	CH ₃	iAm	CO-iBu

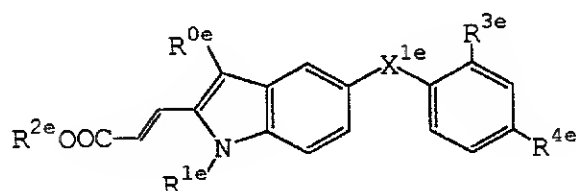
[Table 34]



n^e	X^{1e}	R^{0e}	R^{1e}	R^{2e}	R^{3e}	R^{4e}
0	C(O)	H	iBu	H	O-iBu	O-iBu
0	C(O)	H	iBu	CH ₃	O-iBu	O-iBu
0	C(O)	Br	iBu	H	O-iBu	O-iBu
1	C(O)	NO ₂	iBu	H	O-iBu	O-iBu
1	C(O)	COCH ₃	iBu	H	O-iBu	O-iBu
1	C(O)	COOCH ₃	iBu	H	O-iBu	O-iBu
1	C(O)	NHSO ₂ CH ₃	iBu	H	O-iBu	O-iBu
0	CH(OH)	H	iBu	H	O-iBu	O-iBu
0	CH ₂	H	iBu	H	O-iBu	O-iBu
1	C(O)	H	CH ₂ C ₆ H ₅	H	O-iBu	CO-iBu
1	C(O)	H	C ₆ H ₁₁	H	O-iBu	CO-iBu
1	C(O)	H	C ₆ H ₅	H	O-iBu	CO-iBu
1	C(O)	H	iBu	H	O-iBu	C ₆ H ₅
1	C(O)	H	iBu	H	OCH ₃	CH ₂ C ₆ H ₅

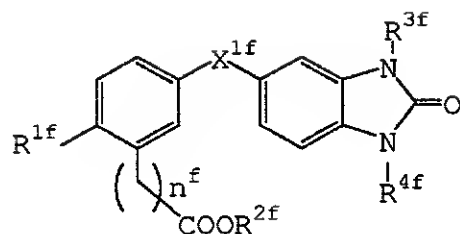
n^e	X^{1e}	R^{0e}	R^{1e}	R^{2e}	R^{3e}	R^{4e}
1	C(O)	H	iBu	H	O-iBu	OC ₆ H ₅
1	C(O)	H	iBu	H	O-iBu	S-iBu
1	C(O)	H	iBu	H	O-iBu	NHSO ₂ CH ₃
1	C(O)	H	iBu	H	O-iBu	2-Py

[Table 35]



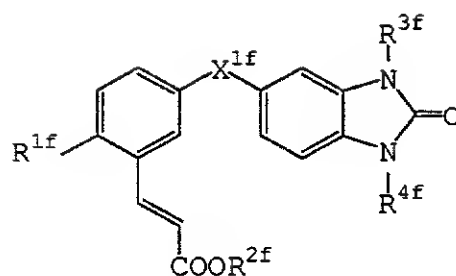
X ^{1e}	R ^{0e}	R ^{1e}	R ^{2e}	R ^{3e}	R ^{4e}
C(O)	H	iBu	H	O-iBu	O-iBu
C(O)	H	iBu	CH ₃	O-iBu	O-iBu
CH(OH)	H	iBu	H	O-iBu	O-iBu
CH ₂	H	iBu	H	O-iBu	O-iBu
C(O)	Cl	iBu	H	O-iBu	O-iBu
C(O)	H	CH ₂ C ₆ H ₅	H	O-iBu	CO-iBu
C(O)	H	C ₆ H ₁₁	H	O-iBu	CO-iBu
C(O)	H	C ₆ H ₅	H	O-iBu	CO-iBu
C(O)	H	iBu	H	O-iBu	C ₆ H ₁₁
C(O)	H	iBu	H	O-iBu	CH ₂ C ₆ H ₅
C(O)	H	iBu	H	O-iBu	S-iBu
C(O)	H	iBu	H	O-iBu	NHSO ₂ CH ₃
C(O)	H	iBu	H	O-iBu	2-Py

[Table 36]



n^f	X^{1f}	R^{1f}	R^{2f}	R^{3f}	R^{4f}
1	C(O)	$\text{CH}_2\text{C}_6\text{H}_5$	H	iAm	iAm
1	C(O)	C_6H_{11}	H	iAm	iAm
1	C(O)	C_6H_5	H	iAm	iAm
1	C(O)	O-iAm	H	iAm	iAm
1	C(O)	OC_6H_5	H	iAm	iAm
1	C(O)	S-iBu	H	iAm	iAm
1	C(O)	$\text{NHSO}_2\text{C}_6\text{H}_5$	H	iAm	iAm
1	CH(OH)	O-iBu	H	iAm	iAm
1	CH_2	O-iBu	H	iAm	iAm
1	C(O)	O-iBu	H	$\text{CH}_2\text{C}_6\text{H}_5$	$\text{CH}_2\text{C}_6\text{H}_5$
1	C(O)	O-iBu	H	C_6H_{11}	iAm
1	C(O)	O-iBu	H	$\text{CH}_2\text{C}_6\text{H}_5$	iAm

[Table 37]



X^{1f}	R^{1f}	R^{2f}	R^{3f}	R^{4f}
C(O)	$CH_2C_6H_5$	H	iAm	iAm
C(O)	C_6H_{11}	H	iAm	iAm
C(O)	C_6H_5	H	iAm	iAm
C(O)	OC_6H_5	H	iAm	iAm
C(O)	S-iBu	H	iAm	iAm
C(O)	$NHSO_2C_6H_5$	H	iAm	iAm
C(O)	O-iBu	H	iAm	iAm
C(O)	O-iBu	H	$CH_2C_6H_5$	$CH_2C_6H_5$
C(O)	O-iBu	H	C_6H_{11}	iAm
C(O)	O-iBu	H	C_6H_5	iAm
C(O)	O-iBu	H	$CH_2C_6H_5$	iAm
CH(OH)	O-iBu	H	iAm	iAm
CH_2	O-iBu	H	iAm	iAm

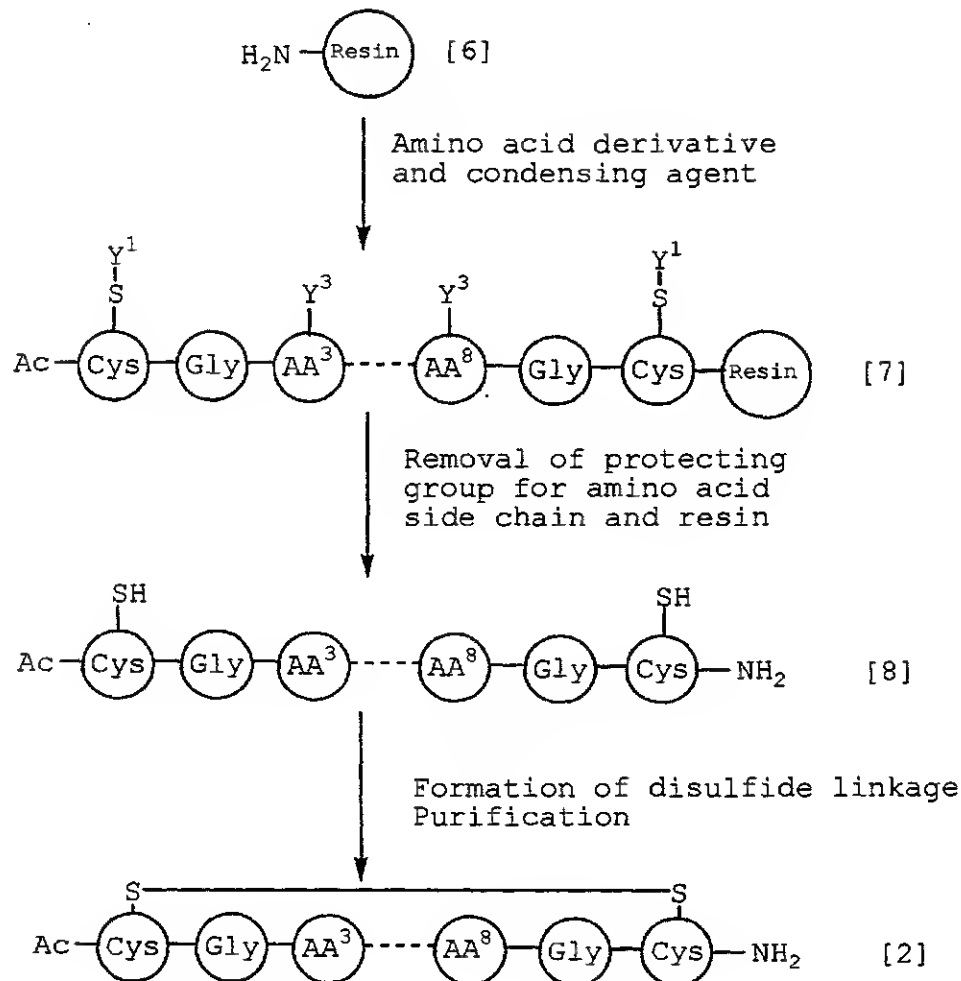
In cases where the compounds conforming to the pharmacophore of formula 1, the compounds of general formulas [2], [2b], [3], [4], [5], [a], [b], [c], [d], [e], [f] and [g] or salts of these compounds
5 have isomers such as optical isomers, geometrical isomers and tautomers, this invention involves these isomers, too, and involves solvated products, hydrated products and crystal of various forms, too.

Next, processes for producing the compounds
10 of this invention will be explained.

The compound of this invention are produced by combining the processes which are well known in themselves, and, for example, according to the Production Processes 1 to 20.

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[Production Process 1]



wherein AA^3 and AA^8 are as defined above, Ac is acetyl group, Y^1 is an optionally used protecting group for cysteine, and Y^3 and Y^8 independently represent a

5 protecting group for functional group in the side chain of amino acid, provided that amino acid residues are expressed according to the three letters expression prescribed in IUPAC and IUB.

The peptide of this invention is produced by a liquid phase method or a solid phase method according to a combination of methods which are well known in themselves (Izumiya et al., Fundamentals and
5 Experiments of Peptide Syntheses, Pages 194-283, published by Maruzen Shuppan).

The peptide-bonded resin of general formula [7] can be obtained by subjecting the resin of general formula [6] to a solid phase method. The construction
10 of peptide chain by solid phase method is carried out by repeating a condensation of amino acid having an amino acid functional group protected with appropriate protecting group and de-protection of the protecting group of α -amino acid. Condensation of amino acid is
15 carried out successively one by one from the terminal amino acid according to the order of amino acids in the sequence to be synthesized. The procedure of the solid phase method will be mentioned below. A series of reactions used therein are preferably carried out in an
20 atmosphere of nitrogen. Any of the manual method and the method of using an automatic synthesizing apparatus may be adopted.

(1) A peptide-bonded resin having a protected N terminal can be obtained by condensing a resin with
25 an amino acid derivative. Concretely speaking, a resin is introduced into a reactor, and a solvent is added to swell the resin. After filtering off the solvent, an amino acid derivative and a condensing agent are added,

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the like are used. Preferable amino acid derivative is Fmoc-amino acid. As the condensing agents which can be used in this reaction, dicyclohexylcarbodiimide, diisopropylcarbodiimide, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP),
5 bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBROP) and the like can be referred to. The condensing agent may be used in an amount of 1-10 equivalents per equivalent of amino group in the resin.

10 When PyBOP or PyBROP is used, an amine such as diisopropylethylamine, triethylamine or the like may be added in an amount of 1-5 equivalents per equivalent of the condensing agent. Further, an active ester-forming agent such as N-hydroxybenzotriazole, N-hydroxy-7-
15 azabenzotriazole or the like may be added in an amount of 0.5-2 equivalents per equivalent of the condensing agent. The reaction is carried out usually at 10-40°C and preferably 20-30°C, for a period of 5-120 minutes.

(2) The peptide of which N terminal is de-
20 protected can be obtained by reacting the α -amino protecting group of peptide-bonded resin having a protected N terminal in the presence of de-protecting agent to eliminate the protecting group. Concretely speaking, a peptide-bonded resin of which N terminal is
25 protected is reacted with an acid or a base in the presence or absence of a solvent.

The de-protecting agent used in this reaction is appropriately selected in accordance with the kind

of α -amino protecting group. When the protecting group of α -amino group is Boc group, an acid such as trifluoroacetic acid, methanesulfonic acid or the like is used. When the protecting group is Fmoc group, a
5 base such as piperidine, 1,8-diazabicyclo[5.4.0]undec-7-ene or the like is used. The solvents used in this reaction are not limited so far as they exercise no adverse influence upon the reaction. When an acid is used, dichloromethane, dichloroethane and the like are
10 used. When a base is used, N,N-dimethylformamide, N-methylpyrrolidone and the like are used. In a case where a solvent is used, the solvent is used in an amount of 5-20 ml per gram of the resin. The reaction is carried out usually at 10-40°C and preferably 20-
15 30°C, for a period of 5-120 minutes.

(3) Peptide-bonded resins having ten residues can be obtained by repeating the procedure of (1) or (2) ten times on the peptide-bonded resin obtained above.

20 (4) The peptide of general formula (7) can be obtained by acetylating a peptide-bonded resin having 10 residues. Concretely, it can be obtained by reacting a peptide-bonded resin of 10 residues with acetic anhydride in the presence or absence of an
25 amine.

In this reaction, acetic anhydride is used in an amount of 1-20 equivalents and preferably 5-10 equivalents per equivalent of amino group in the resin.

As the amine used in this reaction according to the need, diisopropylamine, triethylamine and the like can be referred to, and the amount thereof is 0.2-2 equivalents per equivalent of acetic anhydride.

- 5 Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence upon the reaction, N,N-dimethylformamide, dichloromethane, chloroform, N-methylpyrrolidone and the like are used. These solvents may be used either
- 10 alone or in the form of mixture of two or more. Although the amount of the solvent is not particularly limited, the solvent may be used in an amount of 5-20 ml per gram of resin. The reaction is carried out at 10-40°C and preferably 20-30°C, for a period of 10-120
- 15 minutes.

The peptide of general formula [8] can be obtained by removing the protecting group of amino side chain and the resin from the protected peptide resin of general formula [7] in the presence of an acid.

- 20 The acid used in this reaction can appropriately be selected in accordance with combination of the resin used and the protecting group for amino group. For example, trifluoromethanesulfonic acid, anhydrous hydrogen fluoride, trifluoroacetic acid
- 25 and the like can be used as said acid. When the resin is benzhydrylamine resin, 4-methylbenzhydrylamine resin or the like and the protecting group for amino acid side chain is a group selected from benzyl ester group,

cyclohexyl ester group, benzyl group and 2,6-dibromobenzyl group, trifluoromethanesulfonic acid, anhydrous hydrogen fluoride or the like may be used as said acid. When the resin is Rink amide resin or the like and the protecting group for amino acid side chain is a group selected from t-butyl ester group, t-butyl group and trityl group, trifluoroacetic acid and the like may be used as said acid. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, dichloromethane may be used, for example, as said acid. Although amount of the solvent is not critical, it may be 5-100 ml per gram of resin. In this reaction, anisole, thioanisole, m-cresol, p-cresol, ethanedithiol, water, etc. may be added, and the amount thereof is preferably 0.1-20% by volume based on the solvent used. A combined use of these compounds is also allowable, if desired. This reaction is carried out at -10°C to 40°C and preferably 0-20°C, for a period of 30-300 minutes.

The cyclic peptide of general formula [2] can be obtained by forming a disulfide linkage between the cysteine side chains of the peptide of general formula [8]. The formation of intramolecular disulfide linkage between two cysteine residues can be effected according to a known method.

Concretely speaking, when the side chain thiol group of cysteine is not protected, air oxidation

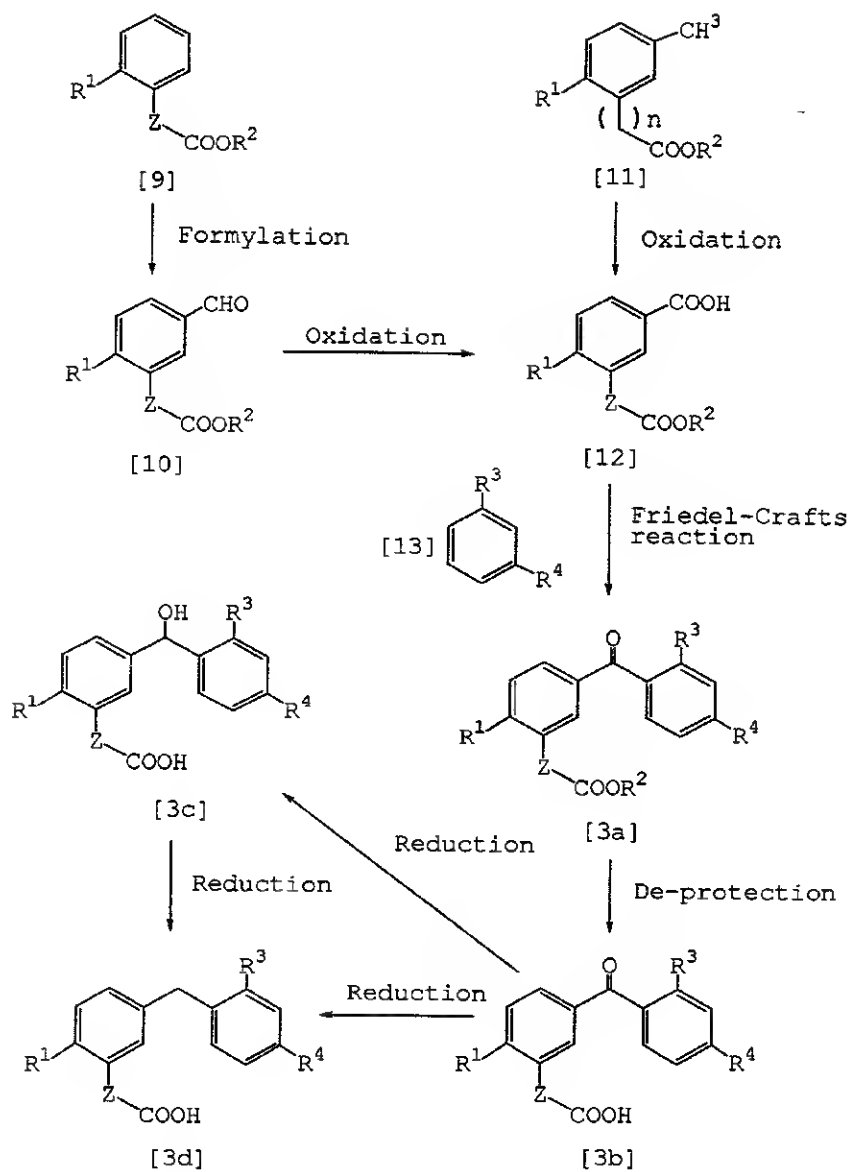
in a dilute aqueous ammonia solution, or the method of using 5-20% dimethyl sulfoxide/trifluoroacetic acid solution may be used. When the side chain thiol group of cysteine is protected with triacetamidomethyl group or the like, the iodine oxidation method or the method of de-protection using silver tetrafluoroborate followed by air oxidation may be used. When the side chain thiol group of cysteine is protected with t-butyl, the silyl chloride-diphenyl sulfoxide method may be used (Development of Pharmaceuticals, Peptide syntheses, Hirokawa Shoten, Pages 233-258).

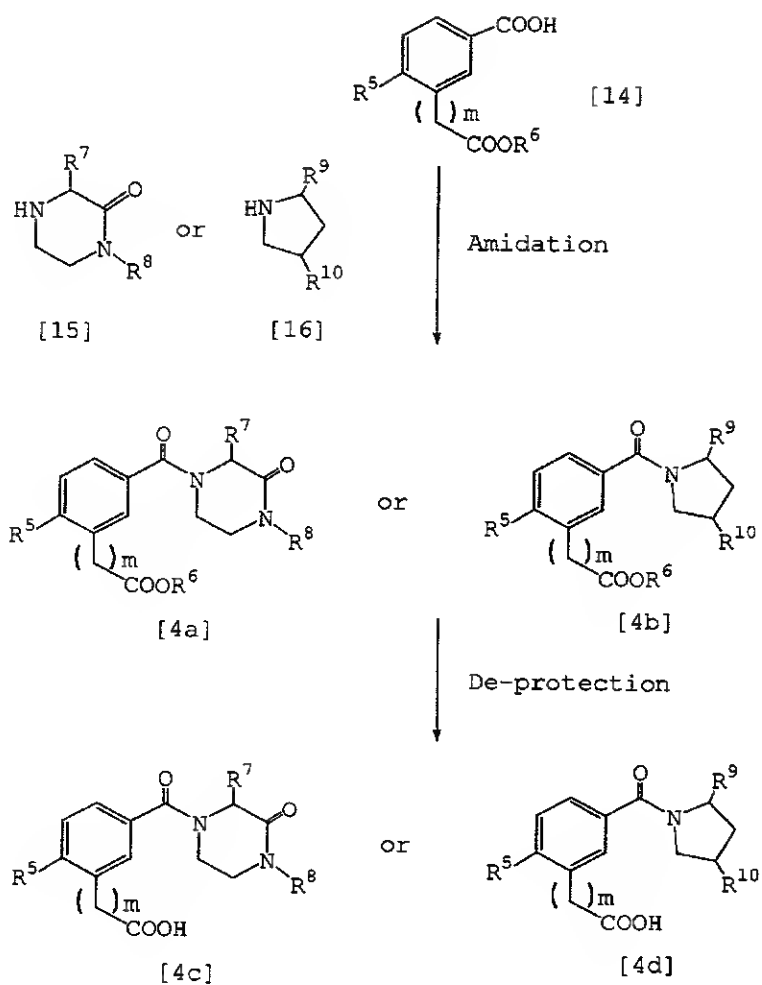
The cyclic peptides of general formula [2] or salts thereof thus obtained can be isolated and purified according to conventional methods such as extraction, crystallization, gel filtration, liquid chromatography and/or column chromatography. For example, the isolation and purification can be effected by the gel filtration method using a gel filter such as Sephadex G-10, G-25 or the like, the column chromatography using a reverse phase type synthetic polymer resin or a chemically modified silica gel carrier and/or a high performance liquid chromatography, or the like.

[Production Process 1a]

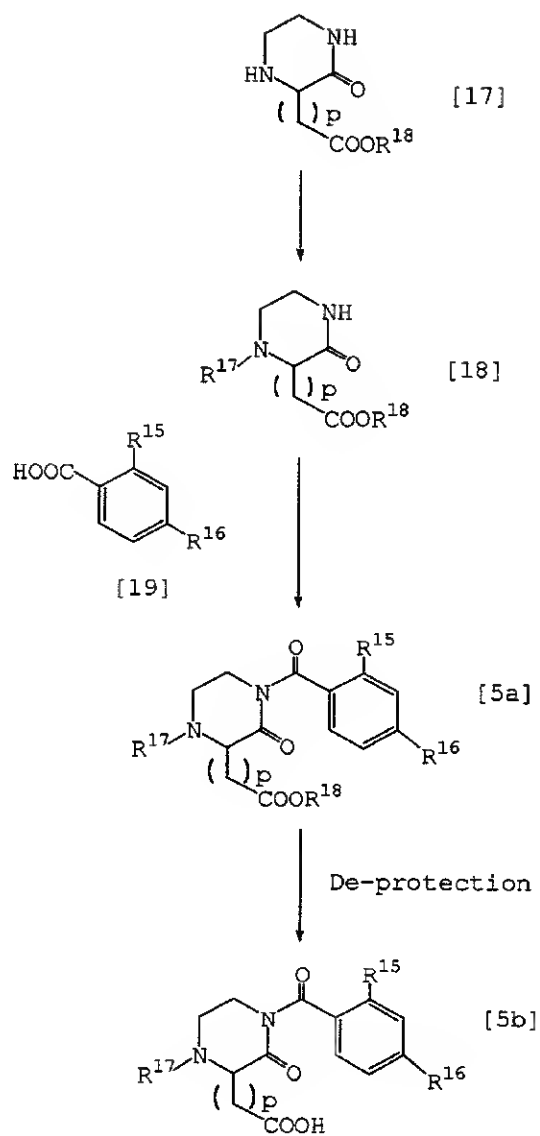
The cyclic peptide of general formula [2b] can be obtained by the same method as Production Process 1.

[Production Process 2]



[illegible]

[Production Process 4]



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wherein R^1 , R^2 (hydrogen atom is excepted), R^3 , R^4 , R^5 , R^6 (hydrogen atom is excepted), R^7 , R^8 , R^9 , R^{10} , R^{15} , R^{16} , R^{17} , R^{18} (hydrogen atom is excepted), Z , n , m and p are as defined above.

5 [Production Process 2]

The compound of general formula [10] can be obtained by reacting a compound of general formula [9] and a formylating agent in the presence of an acid. As the acid used in this reaction, titanium tetrachloride, stannic chloride, aluminum chloride, phosphorus
10 oxychloride and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of formula [9]. As the formylating agent, α,α -dichloromethyl methyl ether, N,N -dimethylformamide, ethyl orthoformate and the like can be referred to, and
15 amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [9]. As the solvent used in this reaction, halogenated hydrocarbons such as methylene chloride, chloroform, carbon
20 tetrachloride and the like and aliphatic hydrocarbons such as n -hexane, cyclohexane and the like can be referred to, and these solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature
25 ranging from -78°C to reflux temperature of the solvent and preferably at $0-30^\circ\text{C}$, for a period of 30 minutes to 24 hours.

The compound of general formula [12] can be

obtained by reacting a compound of general formula [10] with an oxidant in the presence or absence of an acid or a base.

As the acid which can be used in this
5 reaction according to need, hydrochloric acid, sulfuric acid, acetic acid, sulfamic acid and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [10]. As the base which can be used according
10 to need, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide and the like and pyridine and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [10]. As the
15 oxidant used in this reaction, sodium chlorite, sodium hypochlorite, chromic acid, potassium permanganate, hydrogen peroxide, ruthenium oxide, nickel oxide, silver oxide, silver nitrate and the like can be referred to, and amount thereof is 1-10 mol and
20 preferably 1-3 mol per mol of the compound of general formula [10]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, ethers such as tetrahydrofuran, ethyl ether, dioxane and the
25 like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane

and the like, aromatic hydrocarbons such as toluene, benzene and the like, dimethyl sulfoxide, pyridine, water, etc. can be referred to. These solvents may be used either alone or in the form of mixture of two or
5 more. This reaction is carried out usually at a temperature ranging from 0°C to reflux temperature of the solvent for a period of 30 minutes to 24 hours.

The compound of general formula [12] can be obtained by reacting a compound of general formula [11]
10 with an oxidant in the presence or absence of an acid or a base.

As the acid which can be used in this reaction according to the need, sulfuric acid, acetic acid and the like can be referred to, and amount
15 thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [11]. As the base which can be used in this reaction according to the need, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide and the like and pyridine and the
20 like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [11]. As the oxidant used in this reaction, chromic acid, potassium permanganate and the like can be referred to, and amount thereof is 1-10 mol
25 and preferably 1-2 mol per mol of the compound of general formula [11]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction,

halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, pyridine, water and the like can be referred to, for example, and these solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature ranging from 0°C to reflux temperature of the solvent, for a period of 30 minutes to 24 hours.

10 The compound of general formula [3a] can be obtained by subjecting an acid chloride or an acid anhydride of a compound of general formula [12] and a compound of general formula [13] to Friedel-Crafts reaction in the presence of an acid.

15 The acid chloride or acid anhydride of the compound of general formula [12] used in this reaction can be obtained by reacting a compound of general formula [12] with an activating agent such as thionyl chloride, oxalyl chloride, phosphorus pentachloride, 20 acetic anhydride, ethyl chloroformate or the like, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [12]. As the acid used in this reaction, stannic chloride, aluminum chloride, boron trifluoride, zinc chloride and the like 25 can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [12]. The compound of general formula [13] is used in an amount of 1-10 mol and preferably 1-2 mol

per mol of the compound of general formula [12]. As the solvent used in this reaction, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, aliphatic

5 hydrocarbons such as n-hexane, cyclohexane and the like, nitrobenzene, carbon disulfide and the like can be referred to, and these solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature
10 ranging from -78°C to reflux temperature of the solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

The compound of general formula [3b] can be obtained by subjecting a compound of general formula
15 [3a] to a de-protecting reaction such as a hydrolysis using an acid or a base, a de-esterification reaction using a salt, a reductive de-esterification reaction including hydrogenation in the presence of metallic catalyst, etc. As the acid which can be used in this
20 reaction, formic acid, hydrochloric acid, sulfuric acid, hydrobromic acid, trifluoroacetic acid, aluminum chloride, trimethyliodosilane and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general
25 formula [3a]. As the base, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide and the like, tetrabutylammonium fluoride and the like can be referred to, and amount thereof is 1-

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1,000 mol and preferably 1-50 mol per mol of the compound of general formula [3a]. As the salt used in this reaction, lithium iodide, sodium chloride and the like can be referred to, and amount thereof is 1-100

5 mol and preferably 1-10 mol per mol of the compound of general formula [3a]. As the catalyst used in the reductive de-esterification reaction, palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001 to 1 mol

10 and preferably 0.01 to 0.5 mol per one mol of the compound of general formula [3a]. As the reductant, hydrogen, formic acid, cyclohexene, zinc and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general

15 formula [3a]. Although the solvent which can be used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, alcohols such as methanol, ethanol, isopropyl alcohol and the like, ethers such as tetrahydrofuran, ethyl

20 ether, dioxane, anisole and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as

25 ethyl acetate and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, dimethyl sulfoxide, N,N-dimethylformamide, nitromethane, pyridine, water, etc. can be used. These solvents may

be used either alone or in the form of mixture of two or more. The reaction is carried out usually at -78°C to 100°C and preferably $5-80^{\circ}\text{C}$, for a period of 10 minutes to 24 hours.

5 The compound of general formula [3c] can be obtained by reacting a compound of general formula [3b] with a reductant in the presence or absence of an acid, a base or a salt. As the acid which can be used in this reaction according to need, hydrochloric acid, 10 sulfuric acid, trifluoroacetic acid, aluminum chloride, boron trifluoride and the like can be referred, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [3b]. As the base which can be used according to the need, alkali 15 metal hydroxides such as sodium hydroxide, potassium hydroxide and the like and pyridine and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3b]. As the salt which can be used according 20 to the need, lithium chloride, magnesium chloride, calcium chloride and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [3b]. As the reductant, sodium borohydride, lithium borohydride, 25 diisobutylaluminum hydride, lithium aluminum hydride and the like can be used, and amount thereof is 0.25-10 mol and preferably 1-8 mol per mol of the compound of general formula [3b]. Although the solvent used in

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this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, ethers
5 such as tetrahydrofuran, ethyl ether and the like, alcohols such as methanol, ethanol, isopropyl alcohol and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, dimethyl
10 sulfoxide, N,N-dimethylformamide, pyridine, water, etc. can be used. These solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature ranging from -78°C to reflux temperature of the solvent and preferably
15 at -78°C to 70°C, for a period of 30 minutes to 24 hours.

The compound of general formula [3d] can be obtained by subjecting a compound of general formula [3b] or [3c] to reduction including hydrogenation using
20 a metallic catalyst, in the presence or absence of an acid, a base or a salt. As the acid which can be used in this reaction according to need, hydrochloric acid, sulfuric acid, trifluoroacetic acid, aluminum chloride, boron trifluoride and the like can be referred, and
25 amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [3b] or [3c]. As the base which can be used according to the need, alkali metal hydroxides such as sodium hydroxide,

potassium hydroxide and the like and pyridine and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3b] or [3c]. As the salt which can be used according to the need, lithium chloride, magnesium chloride, calcium chloride and the like can be referred to, and amount thereof is 1-50 mol and preferably 1-10 mol per mol of the compound of general formula [3b] or [3c]. As the reductant, sodium borohydride, lithium borohydride, diisobutylaluminum hydride, lithium aluminum hydride, triethylsilane, hydrogen, cyclohexene and the like can be used, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [3b] or [3c]. As the catalyst, palladium-carbon, palladium-black, palladium hydroxide and the like can be used, and amount thereof is 0.001-1 mol and preferably 0.01-0.5 mol per mol of the compound of general formula [3b] or [3c]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, ethers such as tetrahydrofuran, ethyl ether and the like, alcohols such as methanol, ethanol, isopropyl alcohol and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, N,N-

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dimethylformamide, acetic acid, pyridine, water, etc.
can be used. These solvents may be used either alone
or in the form of mixture of two or more. The reaction
is carried out usually at a temperature ranging from -
5 78°C to reflux temperature of the solvent and preferably
at 0-30°C, for a period of 30 minutes to 24 hours.

[Production Process 3]

The compound of general formula [4a] or [4b]
can be obtained by reacting a compound of general
10 formula [14] with a compound of general formula [15] or
[16] by the use of a condensing agent in the presence
or absence of an acid or a base. Otherwise, it can be
obtained by reacting an acid chloride or acid anhydride
of a compound of general formula [14] with a compound
15 of general formula [15] or [16].

The acid chloride or acid anhydride of the
compound of general formula [14] used in this reaction
can be obtained by reacting a compound of general
formula [14] with an activating agent such as thionyl
20 chloride, oxalyl chloride, phosphorus pentachloride,
acetic anhydride, ethyl chloroformate and the like.
The activating agent is used in an amount of 1-10 mol
and preferably 1-2 mol per mol of the compound of
general formula [14]. As the acid used in this
25 reaction according to the need, toluenesulfonic acid,
N-hydroxysuccinimide and the like can be referred to,
and amount thereof is 1-10 mol and preferably 1-5 mol
per mol of the compound of general formula [14]. As

the base which can be used according to the need, N,N-dimethylaminopyridine, pyridine, triethylamine and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [14]. As the condensing agent used in this reaction, dicyclohexylcarbodiimide, diphenylphosphoryl acid azide, N,N'-carbonyldiimidazole and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [14]. The compound of general formula [15] or [16] is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [14]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, ethers such as tetrahydrofuran, ethyl ether and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, ketones such as acetone and the like, pyridine, N,N-dimethylformamide, etc. can be used. These solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature ranging from -78°C to reflux temperature of the solvent and preferably at 0-30°C, for

a period of 30 minutes to 24 hours.

The compound of general formula [4c] or [4d] can be obtained by subjecting a compound of general formula [4a] or [4b] to a de-protection reaction such as hydrolysis using an acid or a base, a de-esterification reaction using a salt, a reductive de-esterification reaction including hydrogenation using a metallic catalyst, or the like.

As the acid used in this reaction, formic acid, hydrochloric acid, sulfuric acid, hydrobromic acid, trifluoroacetic acid, aluminum chloride, trimethyliodosilane and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [4a] or [4b]. As the base, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide and the like, tetrabutylammonium fluoride and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-30 mol per mol of the compound of general formula [4a] or [4b]. As the salt used in this reaction, lithium iodide, sodium chloride and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [4a] or [4b]. As the catalyst used in the de-esterification reaction, palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001-1 mol and preferably 0.01-0.5 mol per mol of the compound of general formula

[4a] or [4b]. As the reductant used in this reaction, hydrogen, formic acid, cyclohexene, zinc and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [4a] or [4b]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, alcohols such as methanol, ethanol, isopropyl alcohol and the like, ethers such as tetrahydrofuran, ethyl ether, dioxane, anisole and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, aromatic hydrocarbons such as toluene, benzene, and the like, dimethyl sulfoxide, N,N-dimethylformamide, nitromethane, pyridine, water, etc. can be used, and these solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature ranging from 0°C to reflux temperature of the solvent and preferably at 5-60°C, for a period of 10 minutes to 24 hours.

[Production Process 4]

The compound of general formula [18] can be obtained by reacting a compound of general formula [17] with an acid chloride in the presence or absence of an acid or a base. Otherwise, it can be obtained by

reacting a compound of general formula [17] with a carboxylic acid by the use of a condensing agent.

As the acid used in this reaction according to the need, toluenesulfonic acid, N-hydroxysuccinic acid and the like can be referred to, and amount thereof is 1-10 mol per mol of the compound of general formula [17]. As the base used in this reaction according to the need, N,N-dimethylaminopyridine, pyridine, triethylamine and the like can be referred to, and amount thereof is 1-10 mol per mol of the compound of general formula [17]. The acid chloride or carboxylic acid is used in an amount of 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [17]. As the condensing agent, dicyclohexylcarbodiimide, diphenylphosphoryl acid azide, N,N'-carbonyldiimidazole and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [17]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, ethers such as tetrahydrofuran, ethyl ether and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate

and the like, ketones such as acetone and the like, pyridine, N,N-dimethylformamide, etc. can be referred to. These solvents may be used either alone or in the form of mixture of two or more. This reaction is

5 carried out usually at a temperature ranging from -78°C to reflux temperature of the solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

Further, it is also possible to obtain the compound of general formula [18] by subjecting a

10 compound of general formula [17] to alkylation, amidation or sulfonamidation in the presence or absence of a base.

As the alkylating agent used in this reaction, methyl iodide, benzyl bromide and the like

15 can be referred to. As the amidating agent, acid anhydrides such as acetic anhydride and the like and acyl halogenides such as acetyl chloride, benzoyl chloride and the like can be referred to. As the sulfonamidating agent, sulfonyl halides such as

20 methanesulfonyl chloride, benzenesulfonyl chloride and the like can be referred to. These reagents are used in an amount of 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [17]. As the base used in this reaction according to the need, for

25 example, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like, and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount

thereof is 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [17]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as toluene, benzene, xylene and the like, ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like, esters such as methyl acetate, ethyl acetate and the like, nitriles such as acetonitrile and the like, amides such as N,N-dimethylformamide and the like, and halogenated hydrocarbons such as chloroform, methylene chloride and the like can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at 0-200°C and preferably 10-150°C, for a period of 10 minutes to 24 hours. It is also possible to effect carbamoylation by reacting a compound of general formula [17] with triphosgene in the presence of a base and then treating the resulting active intermediate with aqueous ammonia. The triphosgen is used in an amount of 0.3-20 mol and preferably 1-4 mol per mol of the compound of general formula [17]. As the base used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like can be referred to, and amount thereof is 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [17]. Although the solvent used in

this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, halogenated hydrocarbons such as chloroform, methylene chloride and the like can be used, for example. This
5 reaction is carried out usually at 0-70°C and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

After the reaction, the reaction mixture is treated with 1-50 v/w, preferably 5-15 v/w, of 25% aqueous ammonia to obtain a carbamoylated product.
10 This reaction is carried out usually at 0-100°C and preferably 0-30°C, for a period of 10 minutes to 24 hours.

The compound of general formula [5a] can be obtained by reacting a compound of general formula [18] and a compound of general formula [19] by the use of a
15 condensing agent, in the presence or absence of an acid or a base. Otherwise, it is also possible to obtain the compound of general formula [5a] by reacting an acid chloride or acid anhydride of the compound of
20 general formula [19] with a compound of general formula [18].

The acid chloride or acid anhydride of the compound of general formula [19] used in this reaction can be obtained by reacting a compound of general
25 formula [19] with an activating agent such as thionyl chloride, oxalyl chloride, phosphorus pentachloride, acetic anhydride, ethyl chloroformate or the like, and amount thereof is 1-10 mol and preferably 1-2 mol per

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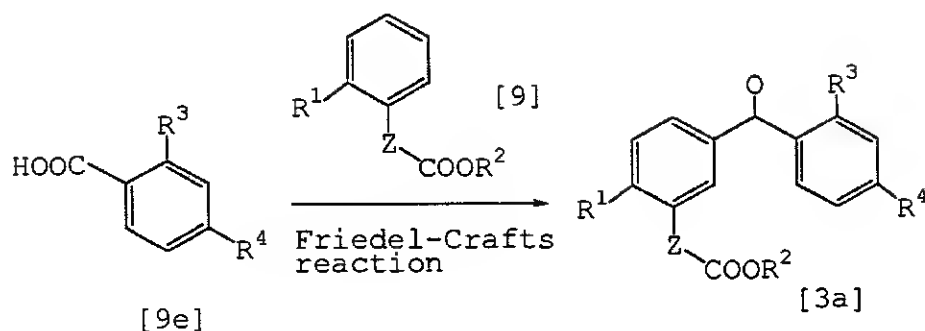
mol of the compound of general formula [19]. As the acid used in this reaction according to the need, toluenesulfonic acid, N-hydroxysuccinimide and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [19]. As the base which can be used in this reaction according to need, N,N-dimethylaminopyridine, pyridine, triethylamine and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [19]. As the condensing agent used in this reaction, dicyclohexylcarbodiimide, diphenylphosphoryl acid azide, N,N'-carbonyldiimidazole and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [19]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, ethers such as tetrahydrofuran, ethyl ether and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, ketones such as acetone and the like, pyridine, N,N-dimethylformamide, etc. can be used. These solvents may be used either alone or in the form

of mixture of two or more. The reaction is carried out at a temperature ranging from -78°C to the reflux temperature of the solvent and preferably at $0-30^{\circ}\text{C}$, for a period of 30 minutes to 24 hours.

5 The compound of general formula [5b] can be obtained by subjecting a compound of general formula [5a] to a de-protecting reaction such as hydrolysis using an acid or a base, de-esterification using a base or reductive de-esterification including hydrogenation
10 using a metallic catalyst. As the acid which can be used in this reaction, formic acid, hydrochloric acid, sulfuric acid, hydrobromic acid, trifluoroacetic acid, aluminum chloride, trimethyliodosilane and the like can be referred to, and amount thereof is 1-1,000 mol and
15 preferably 1-100 mol per mol of the compound of general formula [5a]. As the base, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide and the like, tetrabutylammonium fluoride and the like can be referred to, and amount thereof is 1-
20 1,000 mol and preferably 1-30 mol per mol of the compound of general formula [5a]. As the salt used in this reaction, lithium chloride, sodium chloride and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound
25 of general formula [5a]. As the catalyst used in the reductive de-esterification reaction, palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001 to 1 mol

and preferably 0.01 to 0.5 mol per one mol of the compound of general formula [5a]. As the reductant, hydrogen, formic acid, cyclohexene, zinc and the like can be referred to, and amount thereof is 1-100 mol per 5 mol of the compound of general formula [5a]. Although the solvent which can be used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, alcohols such as methanol, ethanol, isopropyl alcohol and the like, ethers such as 10 tetrahydrofuran, ethyl ether, dioxane, anisole and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane 15 and the like, esters such as ethyl acetate and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, dimethyl sulfoxide, N,N-dimethylformamide, nitromethane, pyridine, water, etc. can be used. These solvents may be used either alone 20 or in the form of mixture of two or more. This reaction is carried out usually at 0°C to reflux temperature of the solvent and preferably 5-60°C, for a period of 10 minutes to 24 hours.

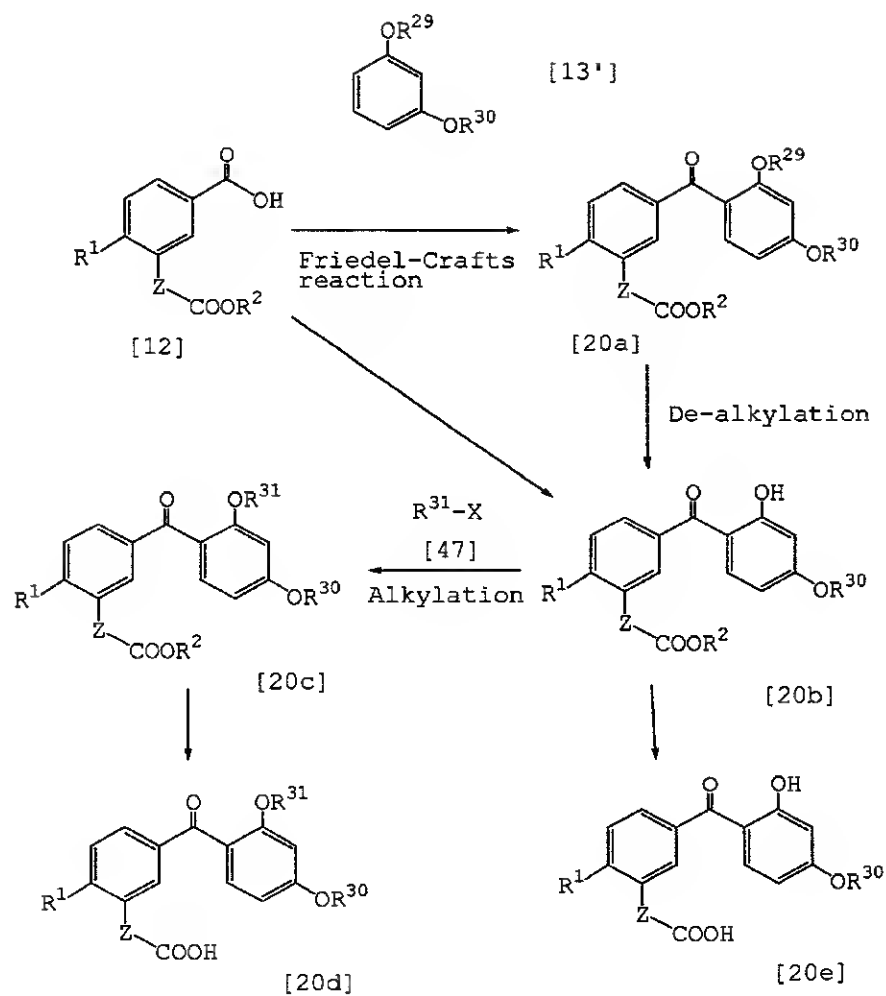
[Production Process 2a]



wherein R¹, R² (hydrogen atom is excepted), R³, R⁴ and Z are as defined above.

The reaction for obtaining a compound of
 5 general formula [3a] from a compound of general formula [9e] may be carried out by the same procedure as that of the reaction for obtaining a compound of general formula [3a] from a compound of general formula [12] described in Production Process 2.

[Production Process 5]



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wherein R^{29} , R^{30} and R^{31} may be the same or different and independently represent unsubstituted or substituted alkyl, cycloalkyl or aralkyl group; X represents halogen atom, alkylsulfonyloxy group or arylsulfonyloxy group; and R^1 , R^2 (hydrogen atom is excepted) and Z are as defined above.

The compound of general formula [20a] can be obtained by subjecting an acid chloride or acid anhydride of a compound of general formula [12] and a compound of general formula [13'] to Friedel-Crafts reaction in the presence of an acid.

The acid chloride or acid anhydride of the compound of general formula [12] used in this reaction can be obtained by reacting a compound of general formula [12] with an activating agent such as thionyl chloride, oxalyl chloride, phosphorus pentachloride, acetic anhydride, ethyl chloroformate or the like, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [12]. As the acid used in this reaction, stannic chloride, aluminum chloride, boron trifluoride, zinc chloride and the like can be referred to, and amount thereof is 0.5-10 mol and preferably 0.9-6 mol per mol of the compound of general formula [12]. The compound of general formula [13'] is used in an amount of 0.1-10 mol and preferably 0.3-3 mol per mol of the compound of general formula [12]. As the solvent used in this reaction, halogenated hydrocarbons such as methylene chloride,

chloroform, carbon tetrachloride and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, nitrobenzene, carbon disulfide and the like can be referred to, and these solvents may be used
5 either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature ranging from -78°C to reflux temperature of the solvent and preferably at -30°C to 30°C, for a period of 10 minutes to 24 hours.

10 It is also possible to obtain a compound of general formula [20b] directly by this reaction while controlling the reaction conditions such as amount of acid, reaction temperature and/or amount of reaction solvent, etc.

15 The compound of general formula [20b] can be obtained by subjecting a compound of general formula [20a] to a de-alkylation reaction in the presence of an acid, a base or a salt.

As the acids which can be used in this
20 reaction, mineral acids such as hydrochloric acid, sulfuric acid, hydrobromic acid and the like, organic acids such as trifluoroacetic acid, thiophenol and the like, and trimethyliodosilane, aluminum chloride, boron trifluoride, zinc chloride and the like can be referred
25 to. As the bases which can be used in this reaction, sodium salt of ethylmercaptan, lithium diisopropylamide and the like can be referred to. As the salts which can be used in this reaction, sodium cyanide, lithium

iodide, pyridine hydrochloride and the like can be referred to. Each of the acids, bases and salts is used in an amount of 1-50 mol and preferably 2-20 mol per mol of the compound of general formula [20a].

- 5 Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol
- 10 diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-
- 15 dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. When a mineral acid is used, water may also be used, if desired. These solvents may
- 20 be used either alone or in the form of mixture of two or more.

This reaction is carried out usually at a temperature ranging from -78°C to reflux temperature of the solvent and preferably at 0-110°C, for a period of

25 30 minutes to 24 hours.

The compound of general formula [20c] can be obtained by subjecting a compound of general formula [20b] to an alkylation reaction with a compound of

general formula [47] in the presence of a base.

In this reaction, the compound of general formula [47] is used in an amount of 1-20 mol and preferably 1-5 mol per mol of the compound of general formula [20b]. As the base used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like; alkali metal hydrides such as sodium hydride and the like; and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount thereof is 1-20 mol and preferably 1-5 mol per mol of the compound of general formula [20b]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. These solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at 0-200°C and preferably at 25-150°C, for a period of 10 minutes to 24 hours.

The compound of general formula [20d] can be obtained by subjecting a compound of general formula [20c] to a de-protecting reaction such as hydrolysis using an acid or a base, de-esterification reaction
5 using a salt, reductive de-esterification reaction including hydrogenation in the presence of metallic catalyst, etc.

As the acid which can be used in this reaction, formic acid, hydrochloric acid, sulfuric
10 acid, hydrobromic acid, trifluoroacetic acid, aluminum chloride, trimethyliodosilane and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [20c]. As the base used in this reaction,
15 alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide and the like, tetrabutylammonium fluoride and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-10 mol per mol of the compound of general
20 formula [20c]. As the salt used in this reaction, lithium iodide, sodium chloride and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [20c]. As the catalyst used in the reductive
25 de-esterification reaction, palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001 to 1 mol and preferably 0.01 to 0.5 mol per mol of the compound

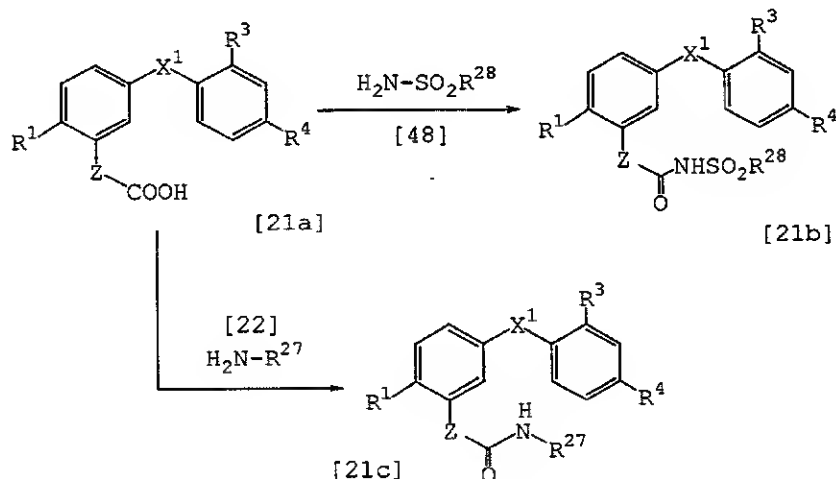
of general formula [20c]. As the reductant, hydrogen, formic acid, cyclohexene, zinc and the like can be referred to, and amount thereof is 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [20c]. Although the solvent which can be used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, alcohols such as methanol, ethanol, isopropyl alcohol and the like, ethers such as tetrahydrofuran, ethyl ether, dioxane, anisole and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, dimethyl sulfoxide, N,N-dimethylformamide, nitromethane, pyridine, water, etc. can be used. These solvents may be used either alone or in the form of mixture of two or more.

The reaction is carried out usually at -78°C to 100°C and preferably $5-60^{\circ}\text{C}$, for a period of 10 minutes to 24 hours.

The reaction for obtaining a compound of general formula [20e] from the compound of general formula [20b] may be effected in the same manner as the procedure for obtaining compound [20d] from compound [20c] in Production Process 5. If desired, the

compound of general formula [20e] can be subjected to the same treatment for producing compound [28c] from compound [28b] in the Production Process 9 to acylate or alkylate the hydroxyl group thereof.

5 [Production Process 6]



wherein R^1 , R^3 , R^4 , Z , X^1 , R^{27} and R^{28} are as defined above.

The compound of general formula [21b] can be obtained by subjecting a compound of general formula [21a] to a reaction with a compound of general formula [48].

This reaction can be carried out by a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an additive, etc. For example, in the method using a base, a condensing agent and an additive, the compound of general formula [48] used in this reaction is

selected from methanesulfonamide, benzenesulfonamide and the like, and amount thereof is 1-10 mol and preferably 1-3 mol per mol of the compound of general formula [21a]. As the base used in this reaction,

5 organic amines such as dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, triethylamine, pyridine, N-methylmorpholine and the like, and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount

10 thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [21a]. As the condensing agent, dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-ethyl-N'-3-dimethylaminopropylcarbodiimide, 1,1'-

15 carbonyldiimidazole, diphenylphosphoryl azide and the like can be used. As the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be used, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general

20 formula [21a]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran,

25 anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-

dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. These solvents may
5 be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

The compound of general formula [21c] can be
10 obtained by subjecting a compound of general formula [21a] and a compound of general formula [22] to an amidation reaction.

This reaction can be effected according to the conventional procedure of amidation. For example,
15 it can be carried out by a method via an acid chloride, a method via an acid anhydride, a method using a base, a condensing agent and an additive, etc. In the method using a base, a condensing agent and an additive, the compound of general formula [22] is used in an amount
20 of 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [21a]. As the base used in this reaction, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like and alkali metal
25 carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [21a]. As the

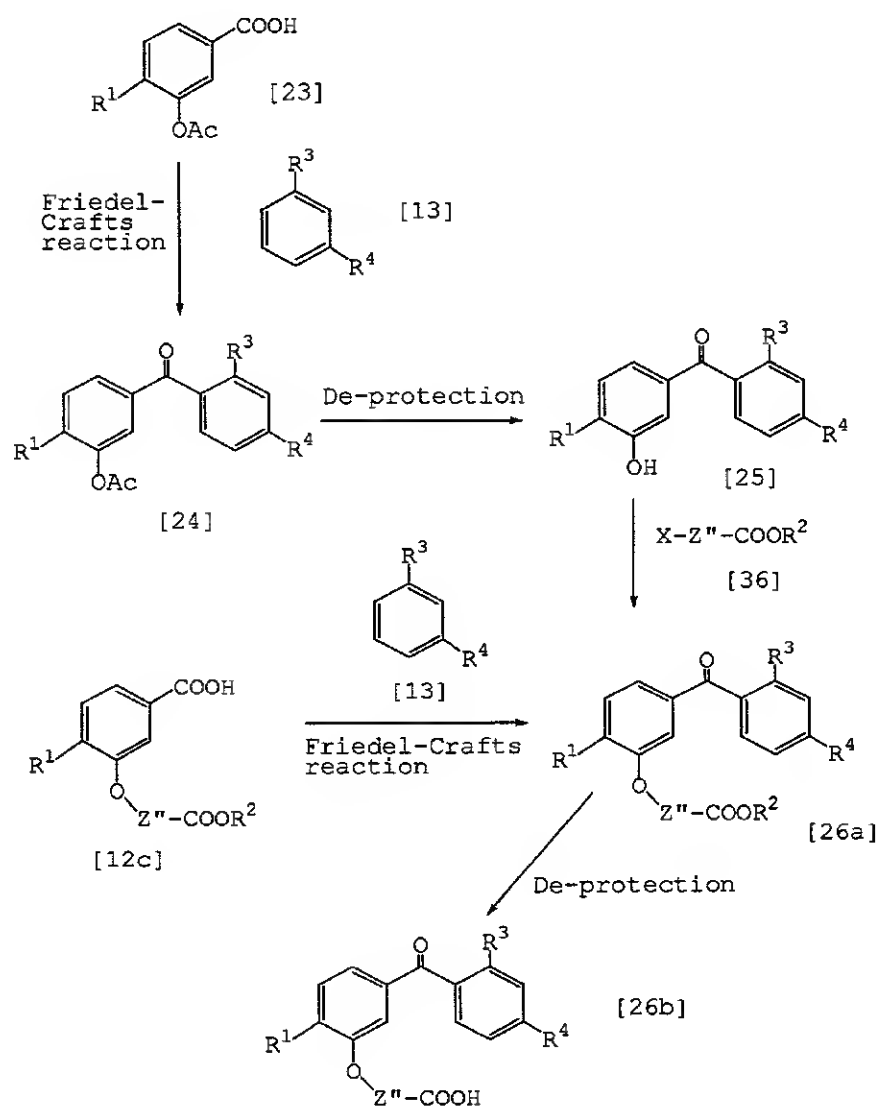
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condensing agent, dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-ethyl-N'-3-dimethylaminopropylcarbodiimide, diphenylphosphoryl azide and the like can be used, and amount thereof is 1-10 mol and preferably 1-2 mol per mol of the compound of general formula [21a]. As the additive, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be used, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [21a]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of -20°C to 150°C and preferably at 0-120°C, for a period of 30 minutes to 24 hours.

In cases where X^1 and R^{27} in the Production Process 6 mentioned above has a group which has to be

protected, such as carboxyl group or the like, the objective compound can be obtained by appropriately protecting the group to be protected before the reaction and carrying out de-protection after completion of the reaction.

[Production Process 7]



wherein Ac is acetyl group; Z" is $-\text{CH}_2-$ or $-\text{CH}_2\text{CH}_2-$; and R^1 , R^2 (hydrogen atom is excepted), R^3 , R^4 and X are as defined above.

The reaction for obtaining a compound of
5 general formula [24] from a compound of general formula [23] is carried out by the same procedure as that for obtaining a compound of formula [20a] from a compound of formula [12] in Production Process 5.

The compound of general formula [25] can be
10 obtained by subjecting a compound of general formula [24] to a de-protection reaction in the presence or absence of an acid or a base.

As the acid used in this reaction according to the need, hydrochloric acid, sulfuric acid, acetic
15 acid, trifluoroacetic acid, p-toluenesulfonic acid and the like can be referred to, and amount thereof is 1-50 mol and preferably 10-30 mol per mol of the compound of general formula [24]. As the base which can be used in this reaction according to the need, alkali metal
20 alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; and alkali
25 metal hydroxides such as sodium hydroxide, potassium hydroxides and the like can be referred to, and the amount thereof is 1-50 mol and preferably 1-30 mol per mol of the compound of general formula [24]. Although

the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, alcohols such as methanol, ethanol and the like; aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; acetic acid; water; and sulfoxides such as dimethyl sulfoxide and the like can be used. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of 0°C to 150°C and preferably at 25-120°C, for a period of 30 minutes to 24 hours.

The reaction for obtaining a compound of general formula [26a] from a compound of general formula [25] is carried out by the same procedure as that for obtaining a compound of formula [20c] from a compound of formula [20b] in Production Process 5.

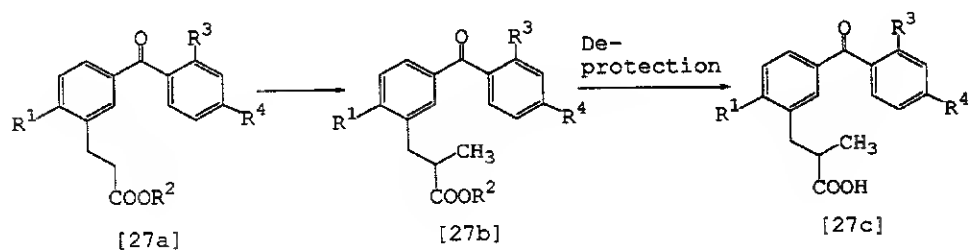
The reaction for obtaining a compound of general formula [26b] from a compound of general formula [26a] is carried out by the same procedure as that for obtaining a compound of formula [20d] from a compound of formula [20c] in Production Process 5.

The reaction for obtaining a compound of

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general formula [26a] from a compound of general formula [12c] is carried out by the same procedure as that for obtaining a compound of formula [24] from a compound of formula [23] in Production Process 7.

5 [Production Process 8a]



wherein R¹, R² (hydrogen atom is excepted), R³ and R⁴ are as defined above.

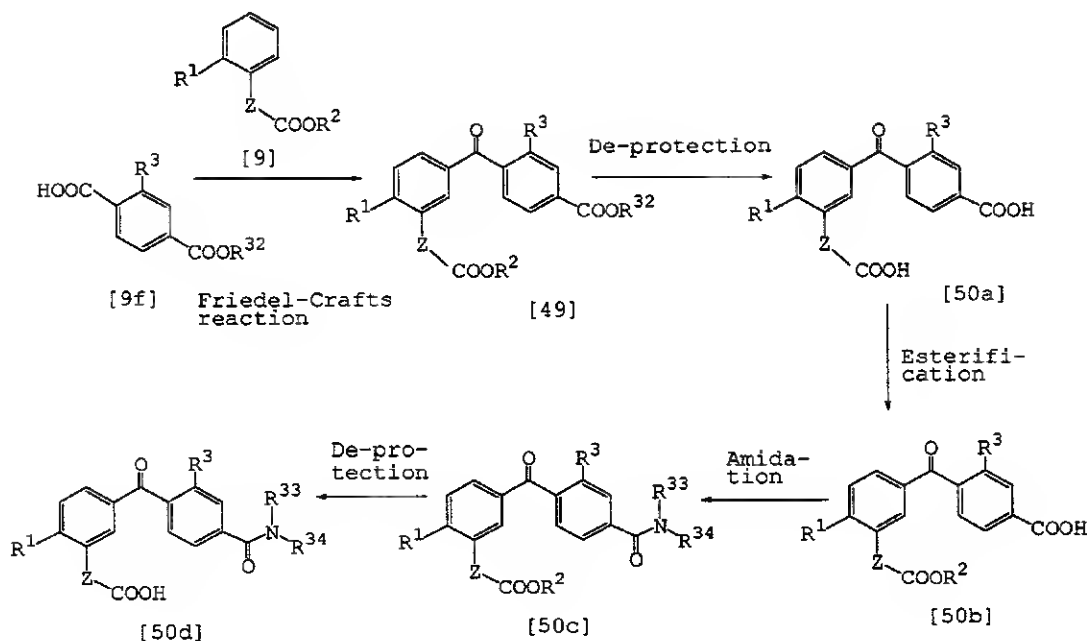
The compound of general formula [27b] can be obtained by reacting a compound of general formula [27a] with methyl iodide, methyl bromide or the like in the presence of a base.

As the base used for this reaction, organolithium compounds such as lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; and alkali metal hydroxides such as sodium hydroxide, potassium hydroxide and the like can be referred to. The base is used in an amount

of 1-20 mol and preferably 1-10 mol per mol of the compound of general formula [27a]. Methyl iodide, methyl bromide and the like are used in an amount of 1-50 mol and preferably 1-20 mol per mol of the compound of general formula [27a]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of -78°C to 150°C and preferably at -60°C to 120°C, for a period of 30 minutes to 24 hours.

The reaction for forming the compound of general formula [27c] from the compound of [27b] is carried out by the same procedure as that for obtaining compound [20d] from compound [20c] in Production Process 5.

[Production Process 8b]



wherein R^{32} is a protecting group for carboxyl group; R^{33} and R^{34} may be the same or different and independently represent hydrogen atom or alkyl, cycloalkyl, aralkyl, aryl or heterocyclic group; and R^1 , R^2 (hydrogen atom is excepted), R^3 and Z are as defined above.

The reaction for forming the compound of general formula [49] from the compound of [9f] is carried out by the same procedure as that for obtaining compound [20a] from compound [12] in Production Process 5.

The reaction for forming the compound of general formula [50a] from the compound of [49] is carried out by the same procedure as that for obtaining

compound [20d] from compound [20c] in Production Process 5.

The compound of general formula [50b] can be obtained by subjecting a compound of general formula [50a] to an esterification reaction.

This reaction can be effected according to the conventional procedure of esterification, and the methods for performing it include a method via an acid chloride, a method via an acid anhydride, a method using a base and alkyl halide, a method using a condensing agent and an additive, etc. When a base and an alkyl halide are used, the bases which can be used in this reaction include, for example, organic amines such as dimethylaminopyridine, triethylamine, N-methylmorpholine and the like; and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like. The amount of said base is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [50a]. As the alkyl halide used in this invention, methyl iodide, ethyl iodide, benzyl bromide and the like can be referred to, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [50a]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl

ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-dimethylformamide and the like; halogenated

- 5 hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. This reaction is carried out usually at a temperature of 0-200°C and preferably at 5-100°C, for a period of 10 minutes to 24 hours. When a
- 10 condensing agent and an additive are used, the intended product can be obtained by subjecting an alcohol such as methanol, ethanol, benzyl alcohol or the like to a condensation reaction with a condensing agent and an additive. As the condensing agent used in this
- 15 reaction, for example, 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-ethyl-N'-3-dimethylaminopropylcarbodiimide, diphenylphosphoryl azide and the like can be referred to. As the additive used in this reaction, for example, 1-
- 20 hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. In this reaction, each of the alcohol, condensing agent and additive is used in an amount of 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [50a]. Although the
- 25 solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane,

5 tetrahydrofuran, anisole, diethylene glycol diethyl
ether, dimethyl cellosolve and the like; esters such as
methyl acetate, ethyl acetate and the like; nitriles
such as acetonitrile and the like; amides such as N,N-
10 dimethylformamide and the like; halogenated
hydrocarbons such as chloroform, methylene chloride and
the like; and sulfoxides such as dimethyl sulfoxide and
the like can be used. The reaction is carried out
usually at 0-200°C and preferably at 5-100°C, for a
15 period of 10 minutes to 24 hours.

The compound of general formula [50c] can be
obtained by subjecting a compound of general formula
[50b] to amidation reaction.

20 This reaction is a conventional amidation
reaction, and includes a method via an acid chloride, a
method via an acid anhydride, a method using a base, a
condensing agent and an additive, etc. In the method
of using a base, a condensing agent and an additive,
the amines used in this reaction include primary amines
25 such as ammonia, methylamine, benzylamine, aniline,
phenethylamine, isopropylamine, aminothiazole and the
like; and secondary amines such as dimethylamine,
diethylamine, di-n-propylamine and the like, and amount
thereof is 0.5-10 mol and preferably 1-3 mol per mol of
the compound of general formula [50b]. As the base
used in this reaction, for example, organic amines such
as dimethylaminopyridine, triethylamine, pyridine, N-
methyldmorpholine and the like; and alkali metal

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carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [50b]. As the

5 condensing agent, dicyclohexylcarbodiimide, diisopropylcarbodiimide, N-ethyl-N'-3-dimethylaminopropylcarbodiimide, diphenylphosphoryl azide and the like can be referred to, and amount thereof is 0.5-10 mol and preferably 1-3 mol per mol of

10 the compound of general formula [50b]. As the additive used in this reaction, for example, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like can be referred to. In this reaction, each of the condensing agent and additive is used in an amount of

15 0.5-10 mol and preferably 1-3 mol per mol of the compound of general formula [50b]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene,

20 toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like; esters such as methyl acetate, ethyl acetate and the like; nitriles such as acetonitrile and the like; amides such as N,N-

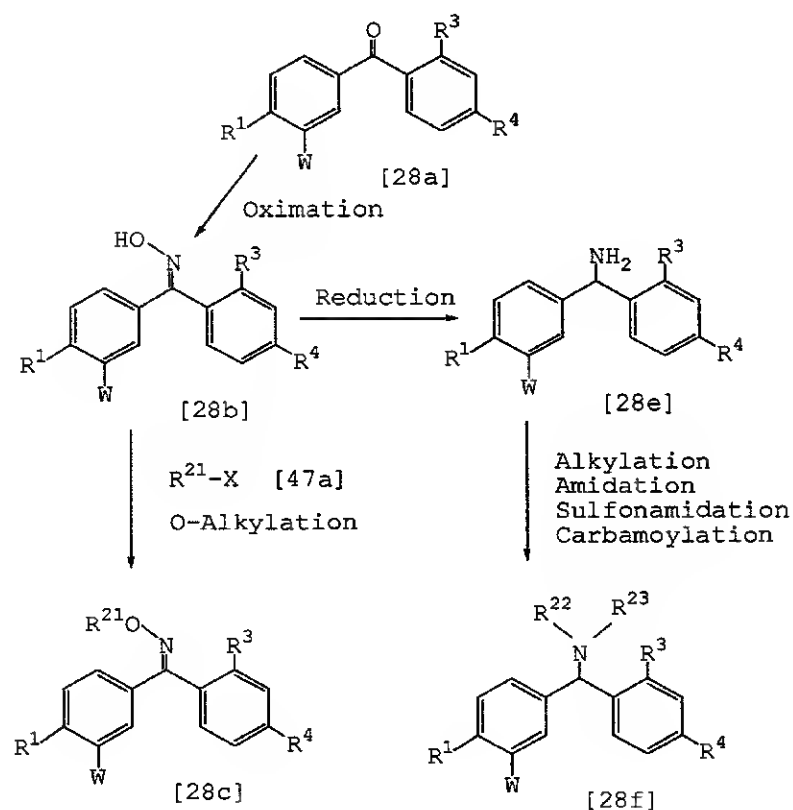
25 dimethylformamide and the like; halogenated hydrocarbons such as chloroform, methylene chloride and the like; and sulfoxides such as dimethyl sulfoxide and the like can be used. The reaction is carried out

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usually at -20°C to 150°C and preferably at $0-120^{\circ}\text{C}$,
for a period of 30 minutes to 24 hours.

The reaction for forming the compound of
general formula [50d] from the compound of [50c] is
5 carried out by the same procedure as that for obtaining
compound [20d] from compound [20c] in Production
Process 5.

[Production Process 9]



wherein R^1 , W, R^3 , R^4 , R^{21} , R^{22} , R^{23} and X are as defined above.

The compound of general formula [28b] can be obtained by reacting a compound of general formula
5 [28a] with hydroxylamine hydrochloride in the presence or absence of a base.

In this reaction, hydroxylamine hydrochloride is used in an amount of 1-10 mol and preferably 1-5 mol per mol of the compound [28a]. As the base used in
10 this reaction, alkali metal hydroxides such as sodium hydroxide and the like, organic amines such as dimethylaminopyridine, triethylamine, pyridine, N-methylmorpholine and the like, and alkali metal carbonates such as potassium carbonate, sodium
15 carbonate and the like can be referred to, and the amount thereof is 0.5-20 mol and preferably 1-10 mol per mol of the compound of general formula [28a]. Although the solvent which can be used in this reaction is not particularly limited so far as it exercises no
20 adverse influence on the reaction, alcohols such as methanol, ethanol, isopropyl alcohol and the like, ethers such as tetrahydrofuran, ethyl ether, dioxane, anisole and the like, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride
25 and the like, nitriles such as acetonitrile and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, aromatic hydrocarbons such as toluene,

benzene, xylene and the like, dimethyl sulfoxide, N,N-dimethylformamide, nitromethane, pyridine, water, etc. can be used. These solvents may be used either alone or in the form of mixture of two or more. The reaction
5 is carried out usually at -20°C to 150°C and preferably $0-120^{\circ}\text{C}$, for a period of 30 minutes to 24 hours.

The compound of general formula [28c] can be obtained by subjecting a compound of general formula [28b] to an O-alkylating reaction or acylation reaction
10 with a compound of general formula [47a] in the presence of base.

In this reaction, the compound of general formula [47a] is used in an amount of 1-20 mol and preferably 1-4 mol per mol of the compound of general
15 formula [28b]. As the base used in this reaction, for example, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like; alkali metal hydrides such as sodium hydride and the like; and alkali metal carbonates such as potassium carbonate,
20 sodium carbonate and the like can be referred to, and amount thereof is 2-20 mol and preferably 1-4 mol per mol of the compound of general formula [28b]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on
25 the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like, esters such as

methanol, ethanol, isopropyl alcohol and the like, amides such as N,N-dimethylformamide and the like, halogenated hydrocarbons such as chloroform, methylene chloride and the like, and sulfoxides such as dimethyl sulfoxide and the like can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at 0-200°C and preferably 10-150°C, for a period of 10 minutes to 24 hours.

The compound of general formula [28e] can be obtained by subjecting a compound of general formula [28b] to reduction including hydrogenation using a metallic catalyst in the presence or absence of an acid, a base or a salt.

As the acid used in this reaction according to the need, hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, nickel chloride, aluminum chloride and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [28b]. As the base used in this reaction according to the need, alkali metal hydroxides such as sodium hydroxide, potassium hydroxide and the like, ammonia, pyridine and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-10 mol per mol of the compound of general formula [28b]. As the salt used in this

reaction according to the need, lithium chloride, magnesium chloride, ammonium acetate and the like can be referred to, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [28b]. As the reductant, sodium borohydride, lithium borohydride, diisobutylaluminum hydride, lithium aluminum hydride, triethylsilane, hydrogen, cyclohexene, diborane, sodium amalgam, Raney nickel and the like can be referred to, and amount thereof is 1-20 mol and preferably 1-10 mol per mol of the compound of general formula [28b]. As the catalyst, palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001-1 mol per mol of the compound [28b]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, halogenated hydrocarbons such as methylene chloride, chloroform, carbon tetrachloride and the like, ethers such as tetrahydrofuran, ethyl ether and the like, alcohols such as methanol, ethanol, isopropyl alcohol and the like, aromatic hydrocarbons such as toluene, benzene, xylene and the like, aliphatic hydrocarbons such as n-hexane, cyclohexane and the like, esters such as ethyl acetate and the like, N,N-dimethylformamide, acetic acid, pyridine water, etc. can be referred to, for example, and these solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out

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The compound of general formula [28f] can be
5 obtained by subjecting a compound of general formula
[28e] to alkylation, amidation or sulfonamidation
reaction in the presence of a base.

As the alkylating agent used in this reaction, for example, methyl iodide and benzyl bromide can be referred to. As the amidating agent, for example, acid anhydrides such as acetic anhydride and the like and acyl halides such as acetyl chloride, benzoyl chloride and the like can be referred to. As the sulfonamidating agent, sulfonyl halides such as methanesulfonyl chloride, benzenesulfonyl chloride and the like can be referred to. These reagents are used in an amount of 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [28e]. As the base used in this reaction, for example, organic amines such as dimethylaminopyridine, triethylamine, pyridine and the like; and alkali metal carbonates such as potassium carbonate, sodium carbonate and the like can be referred to, and amount thereof is 1-20 mol and preferably 1-4 mol per mol of the compound [28e]. Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like, ethers such

as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like, esters such as methyl acetate, ethyl acetate and the like, nitriles such as acetonitrile and the like, alcohols
5 such as methanol, ethanol, isopropyl alcohol and the like, amides such as N,N-dimethylformamide and the like, and halogenated hydrocarbons such as chloroform, methylene chloride and the like can be used as the solvent. These solvents may be used either alone or in
10 the form of mixture of two or more. This reaction is carried out usually at 0-200°C and preferably 10-150°C, for a period of 10 minutes to 24 hours. It is also possible to carry out carbamoylation by reacting a compound of general formula [28e] with triphosgene and
15 then treating the active intermediate thus obtained with aqueous ammonia. The amount of triphosgene used in this reaction is 0.3-20 mol and preferably 1-4 mol per mol of the compound of general formula [28e]. As the base used in this reaction, organic amines such as
20 dimethylaminopyridine, triethylamine, pyridine and the like can be referred to, and amount thereof is 1-20 mol and preferably 1-4 mol per mol of the compound of general formula [28e]. Although the solvent used in this reaction is not particularly limited so far as it
25 exercises no adverse influence on the reaction, halogenated hydrocarbons such as chloroform, methylene chloride and the like are used, for example. This reaction is carried out usually at 0-70°C and preferably

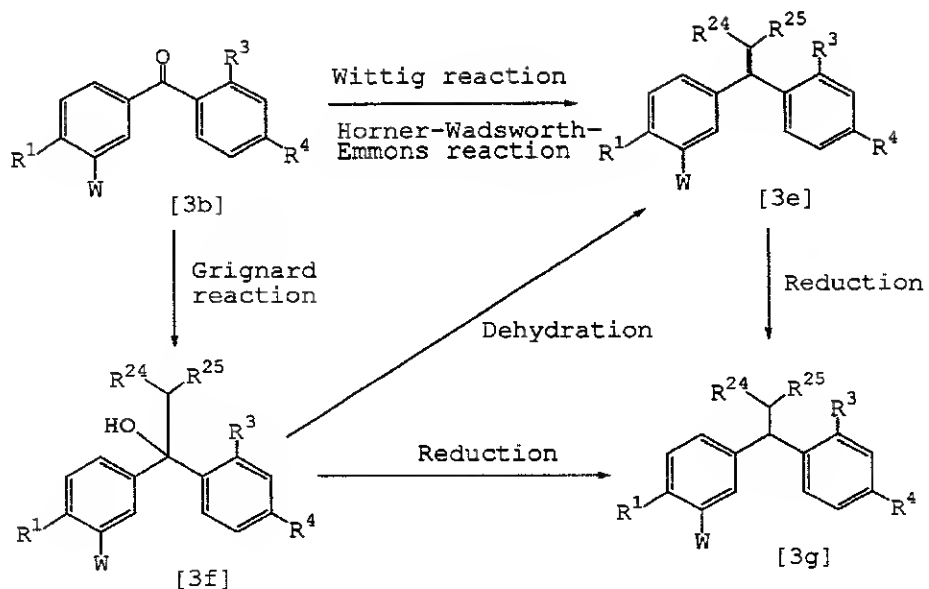
at 0-30°C, for a period of 30 minutes to 24 hours.

Thereafter, the compound of general formula [28e] is treated with 1-50 v/w, preferably 5-15 v/w, of 25% aqueous ammonia to obtain a carbamoyl compound.

- 5 This reaction is carried out usually at 0-100°C and preferably at 0-30°C, for a period of 10 minutes to 24 hours.

- 10 In cases where the compounds mentioned in Production Process 9 have a group which has to be protected, such as a carboxyl group or the like, the objective compound can be obtained by first appropriately protecting the group before the reaction and removing the protecting group after completion of the reaction.

[Production Process 9a]



wherein R^1 , W , R^3 , R^4 , R^{24} and R^{25} are as defined above.

The compound of general formula [3e] can be obtained by reacting a compound of general formula [3b] with Wittig reagent or Horner-Wadsworth-Emmons reagent.

Concretely speaking, the compound of general formula [3e] can be obtained by reacting a compound of general formula [3b] with Wittig reagent synthesized according to the method described in Organic Syntheses Collective Volume, Vol. 5, Pages 751-754 (1973) or Horner-Wadsworth-Emmons reagent synthesized according to the method described in Organic Syntheses Collective Volume, Vol. 5, Pages 509-513 (1973).

The Wittig reagent and Horner-Wadsworth-Emmons reagent used in this reaction are used in an

amount of 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [3b].

Although the solvent used in this reaction is not particularly limited so far as it exercises no
5 adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene and the like, ethers such as dioxane, tetrahydrofuran, diethyl ether and the like, esters such as ethyl acetate, butyl acetate and the like, nitriles such as acetonitrile and
10 the like, amides such as N,N-dimethylformamide N,N-dimethylacetamide and the like, halogenated hydrocarbons such as chloroform, methylene chloride and the like, sulfones such as sulfolane and the like, and sulfoxides such as dimethyl sulfoxide and the like can
15 be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of -78°C to reflux temperature of the solvent and preferably 0-150°C, for a period of 30 minutes to 24
20 hours. If desired, this reaction may be carried out in the atmosphere of an inert gas such as argon or nitrogen.

The compound of general formula [3f] can be obtained by subjecting a compound of general formula
25 [3b] to Grignard reaction.

Concretely speaking, the compound [3f] can be obtained by reacting a compound of general formula [3b] with a Grignard reagent synthesized according to the

method described in Organic Syntheses Collective Volume, Vol. 1, Pages 188-190 (1956).

In this reaction, the Grignard reagent is used in an amount of 1-100 mol and preferably 1-10 mol per mol of the compound of general formula [3b].

Although the solvent used in this reaction is not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene and the like, ethers such as dioxane, tetrahydrofuran, diethyl ether and the like, and sulfones such as sulfolane and the like can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature of -78°C to reflux temperature of the solvent and preferably $0-150^{\circ}\text{C}$, for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in the atmosphere of an inert gas such as argon or nitrogen.

The compound of general formula [3e] can be obtained by dehydrating a compound of general formula [3f] in the presence or absence of an acid, a base or a dehydrating agent.

As the acid used in this reaction, mineral acids such as hydrochloric acid, sulfuric acid, phosphoric acid, hydrobromic acid and the like; and organic acids such as p-toluenesulfonic acid, trifluoroacetic acid and the like can be referred to,

and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3f].

As the base used in this reaction, alkali metal

hydroxides such as sodium hydroxide and the like; and

5 organic amines such as triethylamine, 1,8-diazabicyclo-[5.4.0]undec-7-ene and the like can be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3f]. As the dehydrating agent used in this reaction,

10 diphosphorus pentoxide, polyphosphoric acid and the like can be referred to, and amount thereof 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3f].

Although the solvent used in this reaction is
15 not particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene and the like, ethers such as dioxane, tetrahydrofuran, diethyl ether and the like, esters such as ethyl acetate, butyl
20 acetate and the like, nitriles such as acetonitrile and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, halogenated hydrocarbons such as chloroform, methylene chloride and the like, sulfones such as sulfolane and the like, and
25 sulfoxides such as dimethyl sulfoxide and the like can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. This reaction is carried out usually at a temperature

of -78°C to reflux temperature of the solvent and preferably 0-150°C, for a period of 30 minutes to 24 hours. If desired, this reaction may be carried out in the atmosphere of an inert gas such as argon or
5 nitrogen.

The compound of general formula [3g] can be obtained by subjecting a compound of general formula [3e] or general formula [3f] to a reduction including hydrogenation using a metallic catalyst, in the
10 presence or absence of an acid, a base or a salt.

As the acid used in this reaction, hydrochloric acid, sulfuric acid, hydrobromic acid, aluminum chloride, boron trifluoride, trifluoroacetic acid and the like can be referred to, and amount
15 thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3e] or [3f]. As the base used in this reaction, alkali metal hydroxides such as sodium hydroxide and the like and organic amines such as triethylamine, pyridine and the like can
20 be referred to, and amount thereof is 1-1,000 mol and preferably 1-100 mol per mol of the compound of general formula [3e] or [3f]. As the salt used in this reaction, lithium chloride, calcium chloride and the like can be referred to, and amount thereof is 1-100
25 mol and preferably 1-10 mol per mol of general formula [3e] or [3f]. As the reductant used in this reaction, sodium borohydride, lithium borohydride, lithium aluminum hydride, diisobutylaluminum hydride,

triethylsilane, hydrogen, cyclohexene and the like can be used, and amount thereof is 1-10 mol and preferably 1-5 mol per mol of the compound of general formula [3e] or [3f]. As the catalyst used in this reaction,

- 5 palladium-carbon, palladium-black, palladium hydroxide and the like can be referred to, and amount thereof is 0.001 to 1 mol and preferably 0.01 to 0.5 mol per mol of the compound of general formula [3e] or [3f].

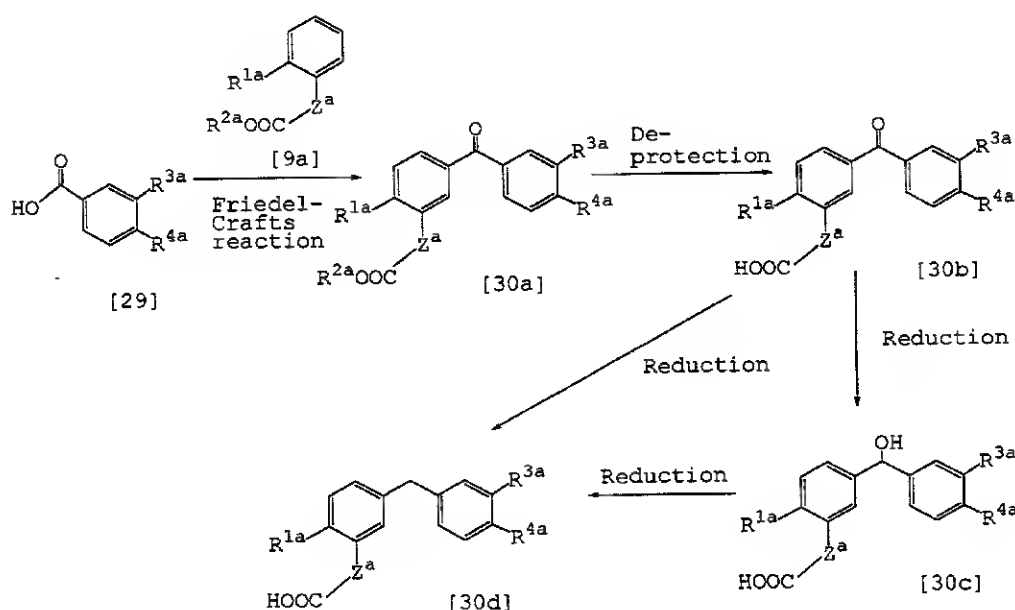
Although the solvent used in this reaction is not

- 10 particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene and the like, ethers such as dioxane, tetrahydrofuran, diethyl ether and the like, esters such as ethyl acetate, butyl acetate and the
15 like, alcohols such as methanol, ethanol and the like, amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, halogenated hydrocarbons such as chloroform, methylene chloride and the like, sulfones such as sulfolane and the like,
20 aliphatic hydrocarbons such as hexane, cyclohexane and the like, acetic acid, pyridine, water, etc. can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature from
25 -78°C to reflux temperature of the solvent and preferably at 0-30°C, for a period of 30 minutes to 24 hours.

When R²⁴ and R²⁵ referred to in the reaction

for obtaining compound [3e], [3f] or [3g] have an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unprotected or protected amino group, the objective compound can be
 5 obtained by appropriately carrying out a protecting reaction and a de-protecting reaction.

[Production Process 10]



wherein R^{1a} , R^{2a} (hydrogen atom is excepted), R^{3a} , R^{4a} and Z^a are as defined above.

10 The reaction for obtaining a compound of general formula [30a] from a compound of general formula [29] can be carried out by the same procedure as that for obtaining a compound of general formula [20a] from compound [12] in Production Process 5.

15 The reaction for obtaining a compound of

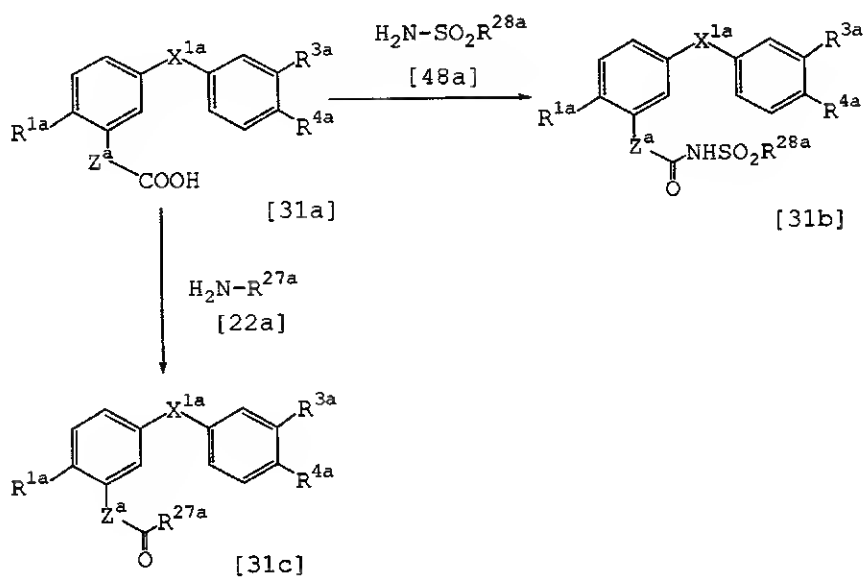
general formula [30b] from a compound of general formula [30a] can be carried out by the same procedure as that for obtaining a compound of general formula [20d] from compound [20c] in Production Process 5.

5 The reaction for obtaining a compound of general formula [30c] from a compound of general formula [30b] can be carried out by the same procedure as that for obtaining a compound of general formula [3c] from compound [3b] in Production Process 2.

10 The reaction for obtaining a compound of general formula [30d] from a compound of general formula [30b] and [30c] can be carried out by the same procedure as that for obtaining a compound of general formula [3d] from compound [3b] and [3c] in Production

15 Process 2.

[Production Process 11]



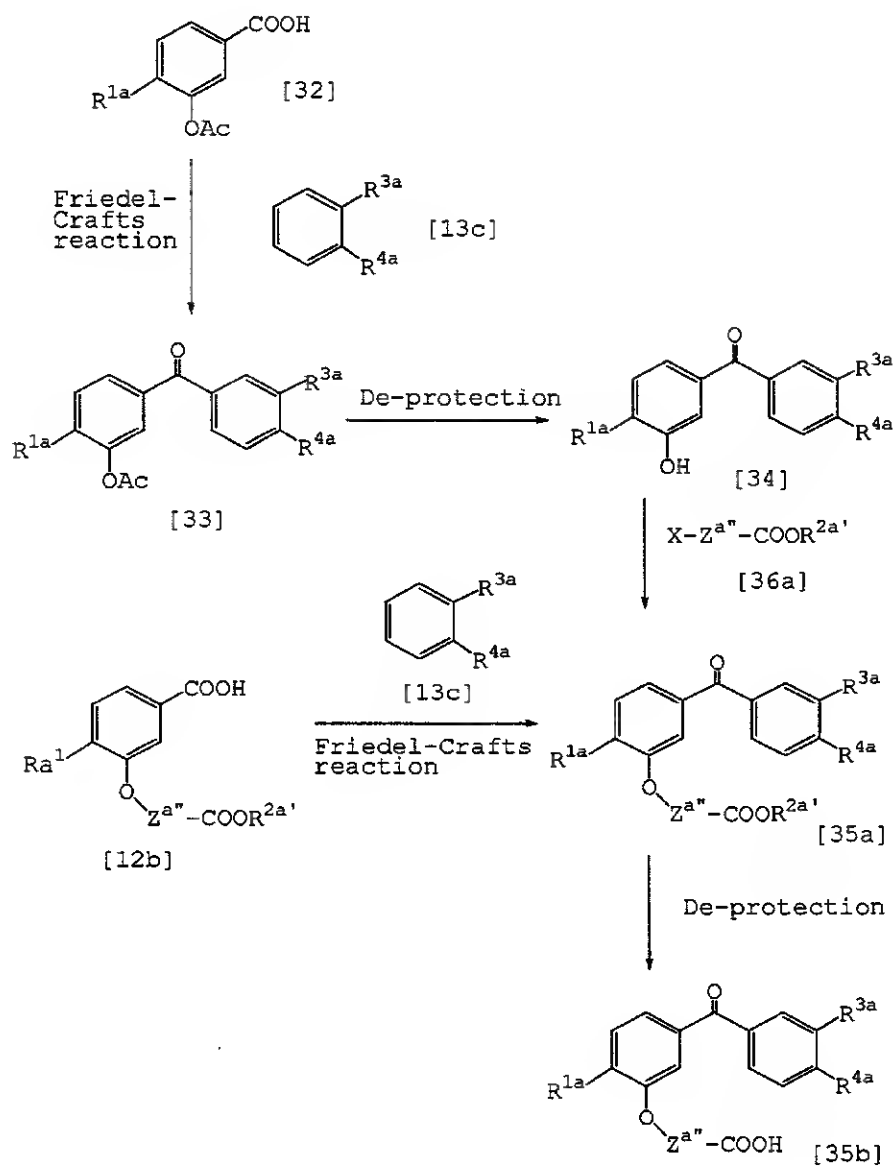
wherein R^{1a} , R^{3a} , R^{4a} , R^{27a} , R^{28a} , X^{1a} and Z^a are as defined above.

The reaction for obtaining a compound of general formula [31b] from a compound of general formula [31a] can be carried out by the same procedure as that for obtaining a compound of general formula [21b] from compound [21a] in Production Process 6.

The reaction for obtaining a compound of general formula [31c] from a compound of general formula [31a] can be carried out by the same procedure as that for obtaining a compound of general formula [21c] from compound [21a] in Production Process 6.

When X^{1a} or R^{27a} described in Production Process 11 has a group which has to be protected such as a carboxyl group, the objective compound can be obtained by appropriately carrying out protection before the reaction and de-protection after completion of the reaction.

[Production Process 12]



wherein Ac represents acetyl group; Z^{a''} represents -CH₂- or -CH₂-CH₂-; and R^{1a}, R^{2a'} (hydrogen atom is excepted), R^{3a}, R^{4a} and X are as defined above.

The reaction for obtaining a compound of
5 general formula [33] from a compound of general formula [32] can be carried out by the same procedure as that for obtaining a compound of general formula [20a] from compound [12] in Production Process 5.

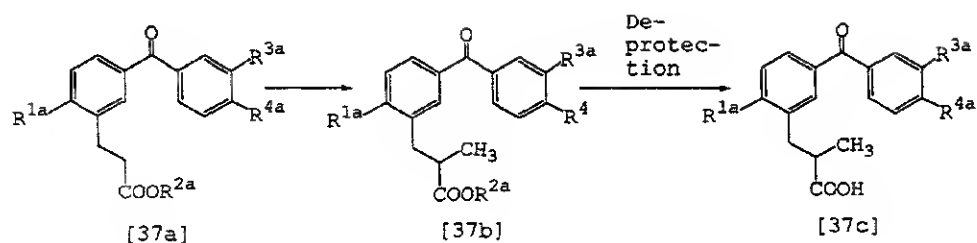
The reaction for obtaining a compound of
10 general formula [34] from a compound of general formula [33] can be carried out by the same procedure as that for obtaining a compound of general formula [25] from compound [24] in Production Process 7.

The reaction for obtaining a compound of
15 general formula [35a] from a compound of general formula [34] can be carried out by the same procedure as that for obtaining a compound of general formula [26a] from compound [25] in Production Process 7.

The reaction for obtaining a compound of
20 general formula [35b] from a compound of general formula [35a] can be carried out by the same procedure as that for obtaining a compound of general formula [26b] from compound [26a] in Production Process 7.

The reaction for obtaining a compound of
25 general formula [35a] from a compound of general formula [12b] can be carried out by the same procedure as that for obtaining a compound of general formula [33] from compound [32] in Production Process 12.

[Production Process 13]

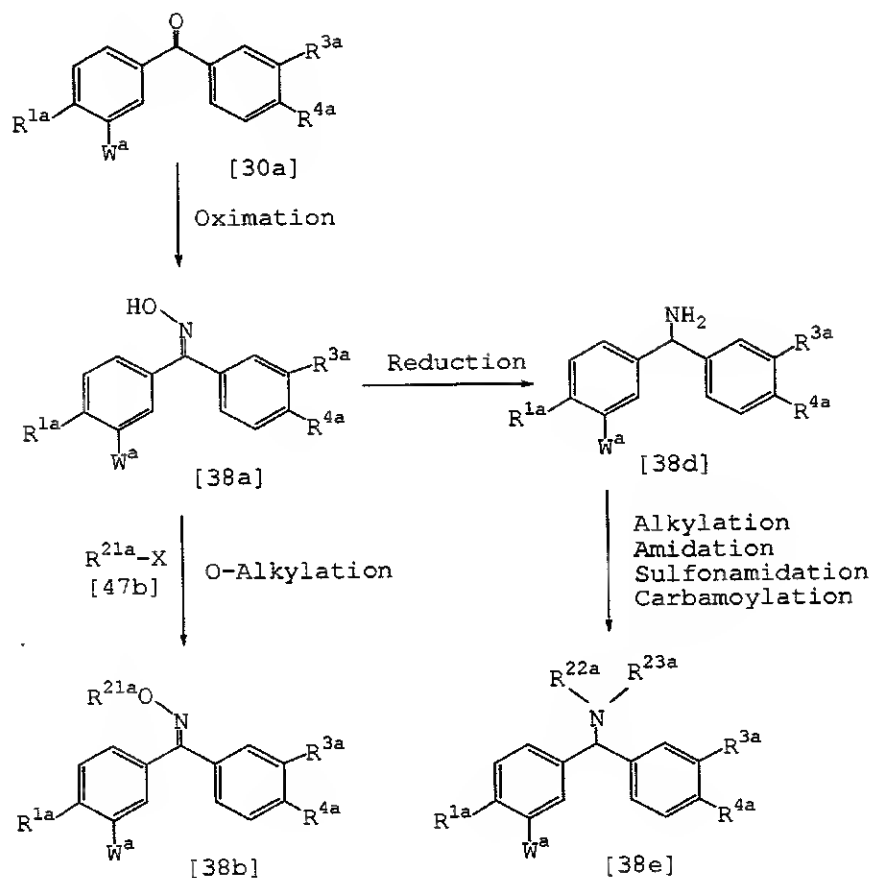


wherein R^{1a} , R^{2a} (hydrogen atom is excepted), R^{3a} and R^{4a} are as defined above.

The reaction for obtaining a compound of
 5 general formula [37b] from a compound of general
 formula [37a] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [27b] from compound [27a] in Production Process 8a.

The reaction for obtaining a compound of
 10 general formula [37c] from a compound of general
 formula [37b] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [27c] from compound [27b] in Production Process 8a.

[Production Process 14]



wherein R^{1a} , W^a , R^{3a} , R^{4a} , R^{21a} , R^{22a} , R^{23a} and X are as defined above.

The reaction for obtaining a compound of general formula [38a] from a compound of general formula [30a] can be carried out by the same procedure as that for obtaining a compound of general formula [28b] from compound [28a] in Production Process 9.

The reaction for obtaining a compound of general formula [38b] from a compound of general

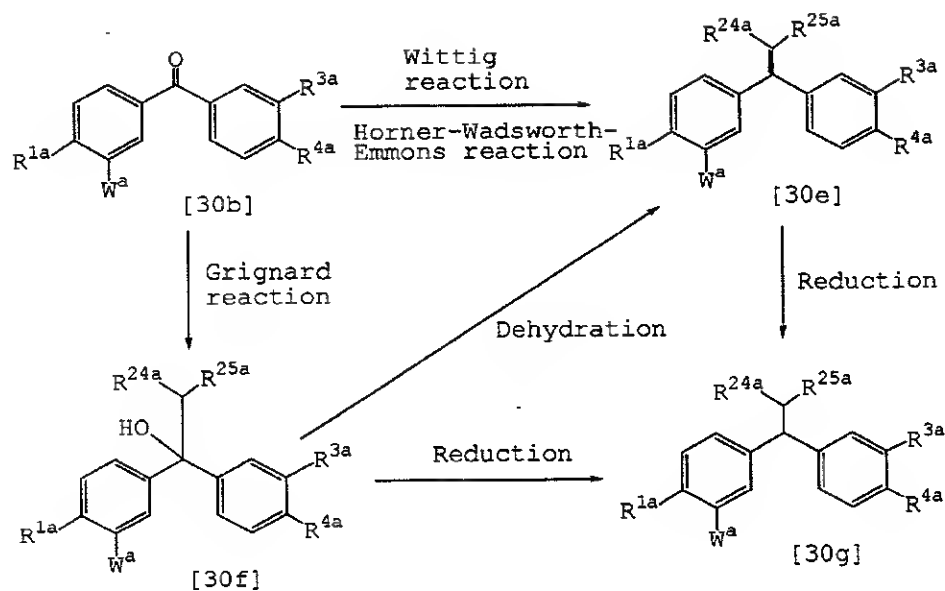
formula [38a] can be carried out by the same procedure as that for obtaining a compound of general formula [28c] from compound [28b] in Production Process 9.

5 The reaction for obtaining a compound of general formula [38d] from a compound of general formula [38a] can be carried out by the same procedure as that for obtaining a compound of general formula [28e] from compound [28b] in Production Process 9.

10 The reaction for obtaining a compound of general formula [38e] from a compound of general formula [38d] can be carried out by the same procedure as that for obtaining a compound of general formula [28f] from compound [28e] in Production Process 9.

15 Some of the compounds mentioned in Production Process 14 may have a group which has to be protected, such as carboxyl group. In such a case, the objective compound can be obtained by carrying out protection before the reaction, then carrying out the reaction, and carrying out de-protection after the reaction.

[Production Process 14a]



wherein R^{1a} , W^a , R^{3a} , R^{4a} , R^{24a} and R^{25a} are as defined above.

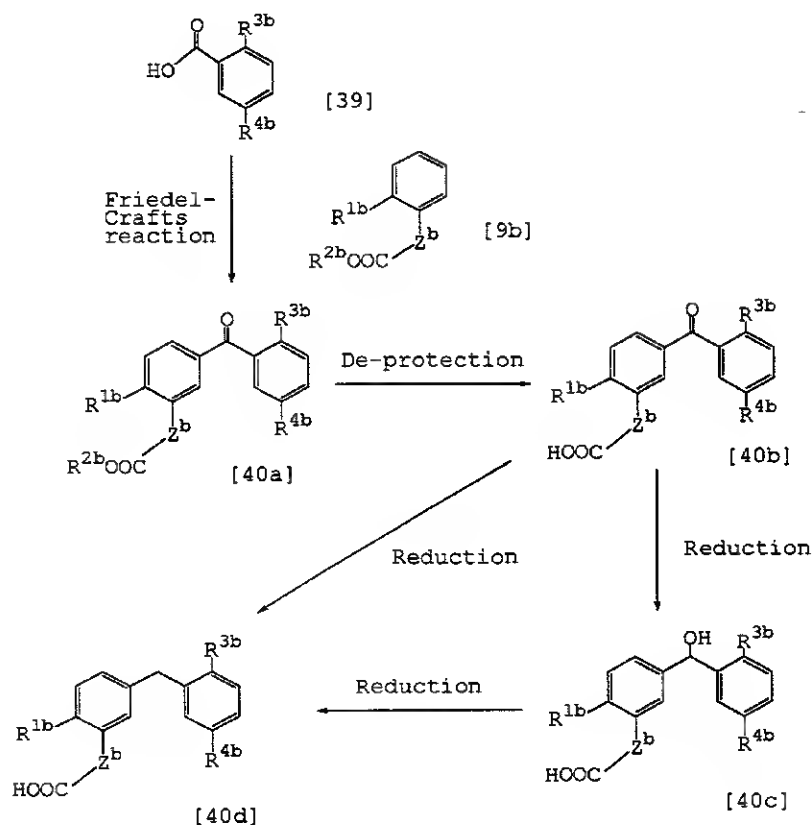
The reaction for obtaining a compound of
 5 general formula [30e] from a compound of general
 formula [30b] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [3e] from compound [3b] in Production Process 9a.

The reaction for obtaining a compound of
 10 general formula [30f] from a compound of general
 formula [30b] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [3f] from compound [3b] in Production Process 9a.

The reaction for obtaining a compound of
 15 general formula [30g] from a compound of general

In some of the reactions for obtaining the compounds of general formulas [30e], [30f] and [30g], R^{24a} and R^{25a} may involve an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group or an unprotected or protected amino group. In such a case, the objective compound can be obtained by carrying out protecting and de-protecting reactions appropriately.

[Production Process 15]



wherein R^{1b} , R^{2b} (hydrogen atom is excepted), R^{3b} , R^{4b} and Z^b are as defined above.

The reaction for obtaining a compound of
 5 general formula [40a] from a compound of general
 formula [39] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [30a] from compound [29] in Production Process 10.

The reaction for obtaining a compound of
 10 general formula [40b] from a compound of general
 formula [40a] can be carried out by the same procedure

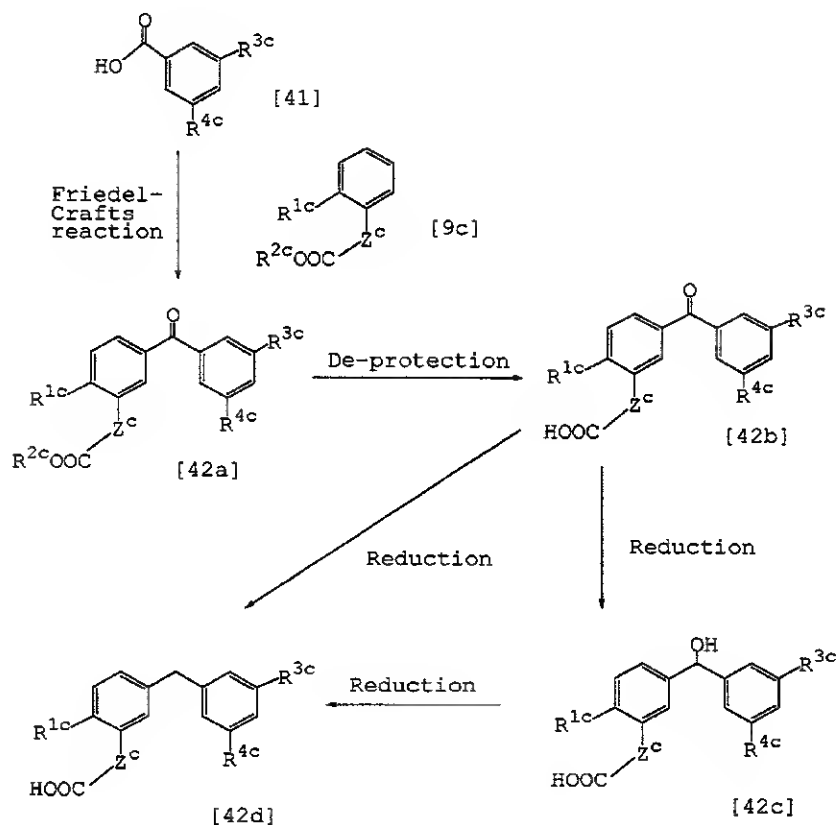
as that for obtaining a compound of general formula [30b] from compound [30a] in Production Process 10.

The reaction for obtaining a compound of general formula [40c] from a compound of general formula [40b] can be carried out by the same procedure as that for obtaining a compound of general formula [30c] from compound [30b] in Production Process 10.

The reaction for obtaining a compound of general formula [40d] from compounds of general formulas [40b] and [40c] can be carried out by the same procedure as that for obtaining a compound of general formula [30d] from compounds [30b] and [30c] in Production Process 10.

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[Production Process 16]



wherein R^{1c} , R^{2c} (hydrogen atom is excepted), R^{3c} , R^{4c} and Z^c are as defined above.

The reaction for obtaining a compound of
 5 general formula [42a] from a compound of general
 formula [41] can be carried out by the same procedure
 as that for obtaining a compound of general formula
 [30a] from compound [29] in Production Process 10

The reaction for obtaining a compound of
 10 general formula [42b] from a compound of general
 formula [42a] can be carried out by the same procedure

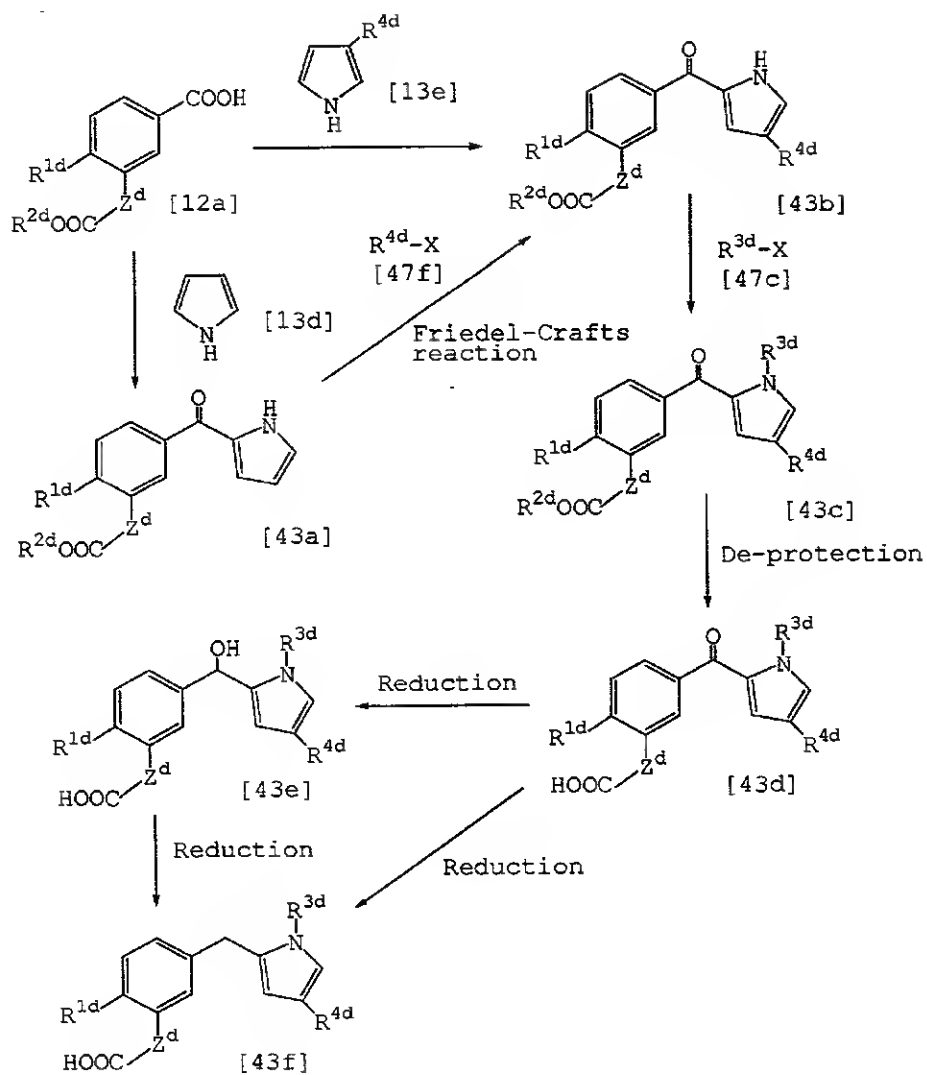
as that for obtaining a compound of general formula [30b] from compound [30a] in Production Process 10.

The reaction for obtaining a compound of general formula [42c] from a compound of general formula [42b] can be carried out by the same procedure as that for obtaining a compound of general formula [30c] from compound [30b] in Production Process 10.

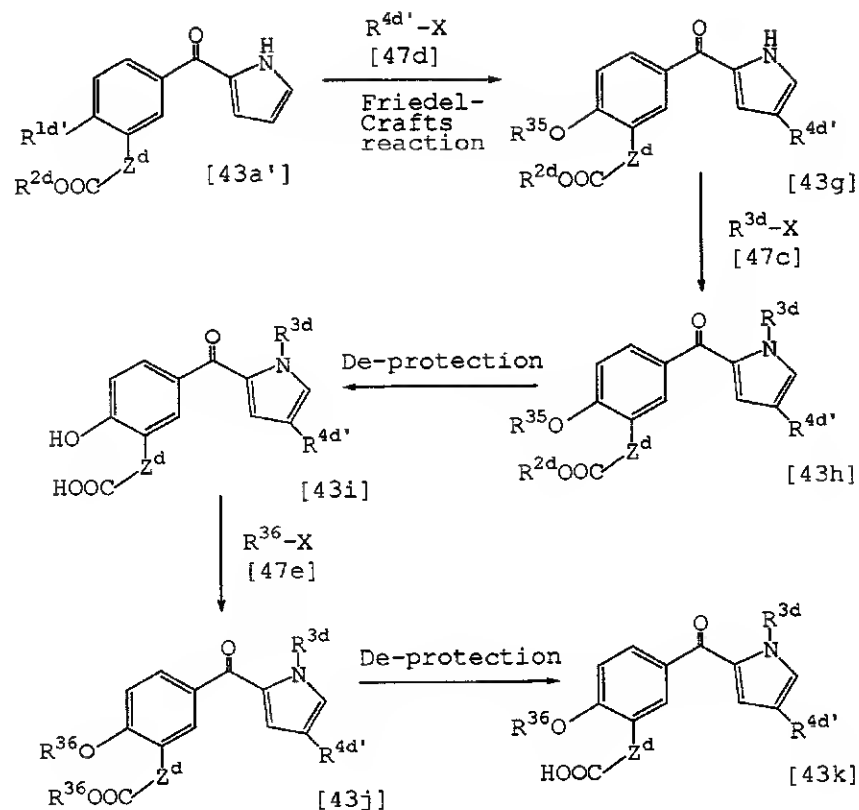
The reaction for obtaining a compound of general formula [42d] from compound of general formulas [42b] and [42c] can be carried out by the same procedure as that for obtaining a compound of general formula [30d] from compounds [30b] and [30c] in Production Process 10.

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wherein R^{1d} , R^{2d} (hydrogen atom is excepted), R^{3d} , R^{4d} , Z^d and X are as defined above.



[Production Process 17a]



wherein $R^{1d'}$ represents alkoxy group; R^{35} represents hydrogen atom or acyl group; R^{36} represents unsubstituted or substituted alkyl, cycloalkyl or aralkyl group; $R^{4d'}$ represents acyl group; and R^{2d} (hydrogen atom is excepted), R^{3d} , X and Z^d are as defined above.

The compound of general formula [43a] can be obtained by reacting an acid chloride or acid anhydride of a compound of general formula [12a] and a compound of general formula [13d] in the presence of a base.

5

This reaction is carried out usually at a

temperature of -78°C to 150°C and preferably at -78°C to 30°C, for a period of 30 minutes to 24 hours.

The reaction for obtaining a compound of general formula [43b] from a compound of [43a] can be carried out by the same procedure as that for obtaining a compound of general formula [20a] from a compound of general formula [12] in Production Process 5.

The reaction for obtaining a compound of general formula [43b] from a compound of [12a] can be carried out by the same procedure as that for obtaining a compound of general formula [43a] from a compound of general formula [12a] in Production Process 17.

The compound of general formula [43c] can be obtained by subjecting a compound of general formula [43b] to an alkylation reaction with and a compound of general formula [47c] in the presence of a base.

In this reaction, the compound of general formula [47c] is used in an amount of 1-20 mol and preferably 1-4 mol per mol of the compound of compound [43b]. As the base used in this reaction, organolithium compounds such as n-butyllithium, phenyllithium, lithium diisopropylamide and the like; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert-butoxide and the like; alkali metal hydrides such as sodium hydride, potassium hydride and the like; alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; and alkali metal hydroxides such as sodium hydroxide,

potassium hydroxide and the like can be referred to, and amount thereof is 2-20 mol and preferably 1-4 mol per mol of the compound of general formula [43b].

Although the solvent used in this reaction is not

- 5 particularly limited so far as it exercises no adverse influence on the reaction, aromatic hydrocarbons such as benzene, toluene, xylene and the like; ethers such as dioxane, tetrahydrofuran, anisole, diethylene glycol diethyl ether, dimethyl cellosolve and the like;
- 10 nitriles such as acetonitrile and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide and the like; halogenated hydrocarbons such as chloroform. methylene chloride and the like; and sulfoxides such as
- 15 dimethyl sulfoxide and the like can be used as the solvent. These solvents may be used either alone or in the form of mixture of two or more. The reaction is carried out usually at a temperature ranging from -78°C to 200°C and preferably at -50°C to 120°C, for a period
- 20 of 10 minutes to 24 hours.

The reaction for obtaining a compound of general formula [43d] from a compound of general formula [43c] is carried out by the same procedure as that for obtaining compound of general formula [20d]

25 from compound of general formula [20c] in Production Process 5.

The reaction for obtaining a compound of general formula [43e] from a compound of general

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formula [43d] is carried out by the same procedure as that for obtaining compound of general formula [3c] from compound of general formula [3b] in Production Process 2.

5 The reaction for obtaining a compound of general formula [43f] from compounds of general formulas [43d] and [43e] is carried out by the same procedure as that for obtaining compound of general formula [3d] from compounds of general formulas of [3b] and [3c] in Production Process 2.

10 The reaction for obtaining a compound of general formula [43g] from a compound of general formula [43a'] is carried out by the same procedure as that for obtaining compound of general formula [43b] from compound of general formula [43a] in Production Process 17.

15 The reaction for obtaining a compound of general formula [43h] from a compound of general formula [43g] is carried out by the same procedure as that for obtaining compound of general formula [43c] from compound of general formula [43b] in Production Process 17.

20 The reaction for obtaining a compound of general formula [43i] from a compound of general formula [43h] is carried out by the same procedure as that for obtaining compound of general formula [43d] from compound of general formula [43c] in Production Process 17.

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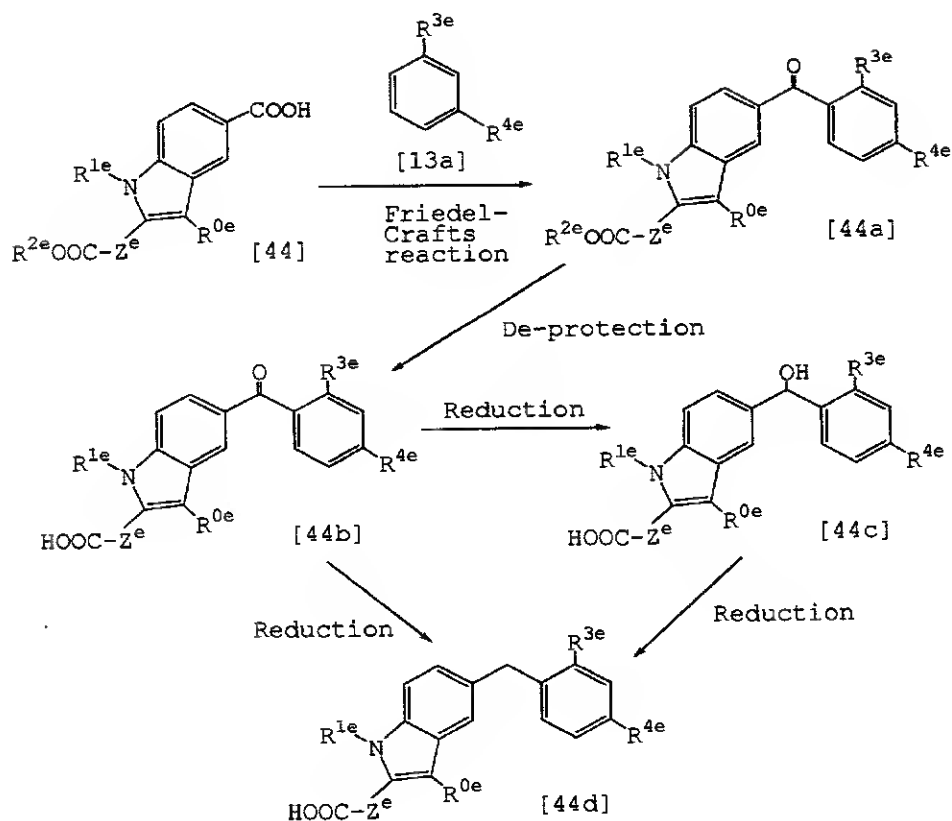
The compound of general formula [43j] can be obtained by subjecting a compound of general formula [43i] to an O-alkylation reaction.

5 The reaction for obtaining a compound of general formula [43j] from a compound of general formula [43i] is carried out by the same procedure as that for obtaining compound of general formula [28c] from compound of general formula [28b] in Production Process 9.

10 The reaction for obtaining a compound of general formula [43k] from a compound of general formula [43j] is carried out by the same procedure as that for obtaining compound of general formula [20d] from compound of general formula [20c] in Production
15 Process 5.

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[Production Process 18]



wherein R^{0e} , R^{1e} , R^{2e} (hydrogen atom is excepted), R^{3e} , R^{4e} and Z^e are as defined above.

The reaction for obtaining a compound of
 5 general formula [44a] from a compound of general
 formula [44] is carried out by the same procedure as
 that for obtaining compound of general formula [30a]
 from compound of general formula [29] in Production
 Process 10.

10 The reaction for obtaining a compound of
 general formula [44b] from a compound of general

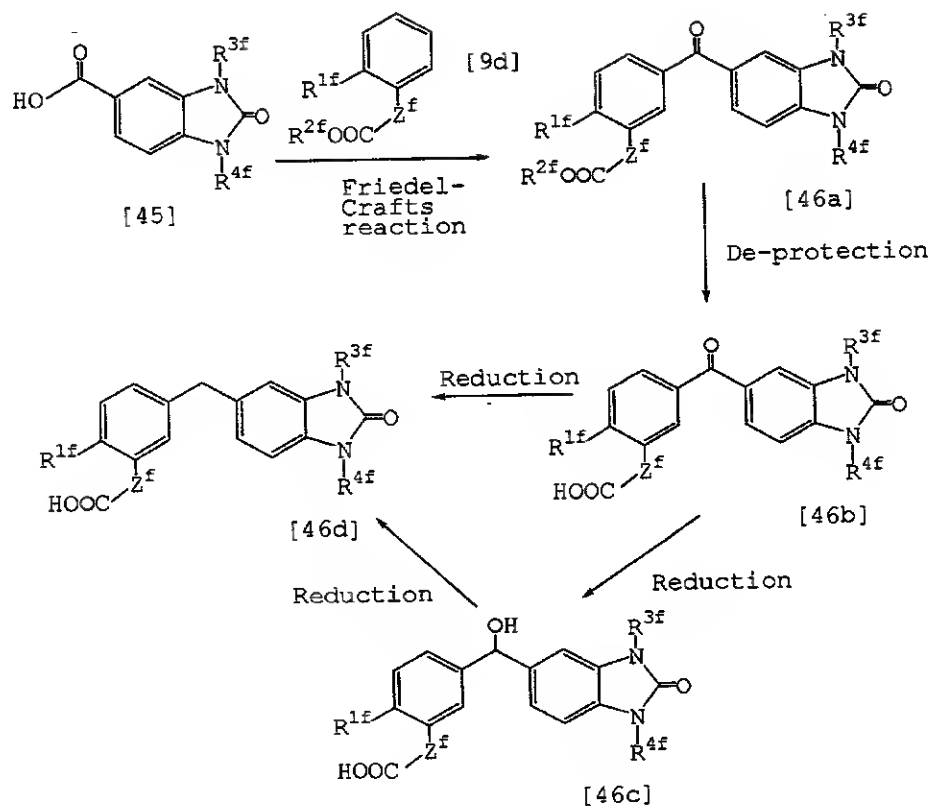
formula [44a] is carried out by the same procedure as that for obtaining compound of general formula [30b] from compound of general formula [30a] in Production Process 10.

5 The reaction for obtaining a compound of general formula [44c] from a compound of general formula [44b] is carried out by the same procedure as that for obtaining compound of general formula [30c] from compound of general formula [30b] in Production
10 Process 10.

 The reaction for obtaining a compound of general formula [44d] from compounds of general formulas [44b] and [44c] is carried out by the same procedure as that for obtaining compound of general
15 formula [30d] from compounds of general formulas [30b] and [30c] in Production Process 10.

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[Production Process 19]



wherein R^{1f} , R^{2f} (hydrogen atom is excepted), R^{3f} , R^{4f} and Z^f are as defined above.

The reaction for obtaining a compound of general formula [46a] from a compound of general formula [45] is carried out by the same procedure as that for obtaining a compound of general formula [30a] from a compound of general formula [29] in Production Process 10.

The reaction for obtaining a compound of general formula [46b] from a compound of general

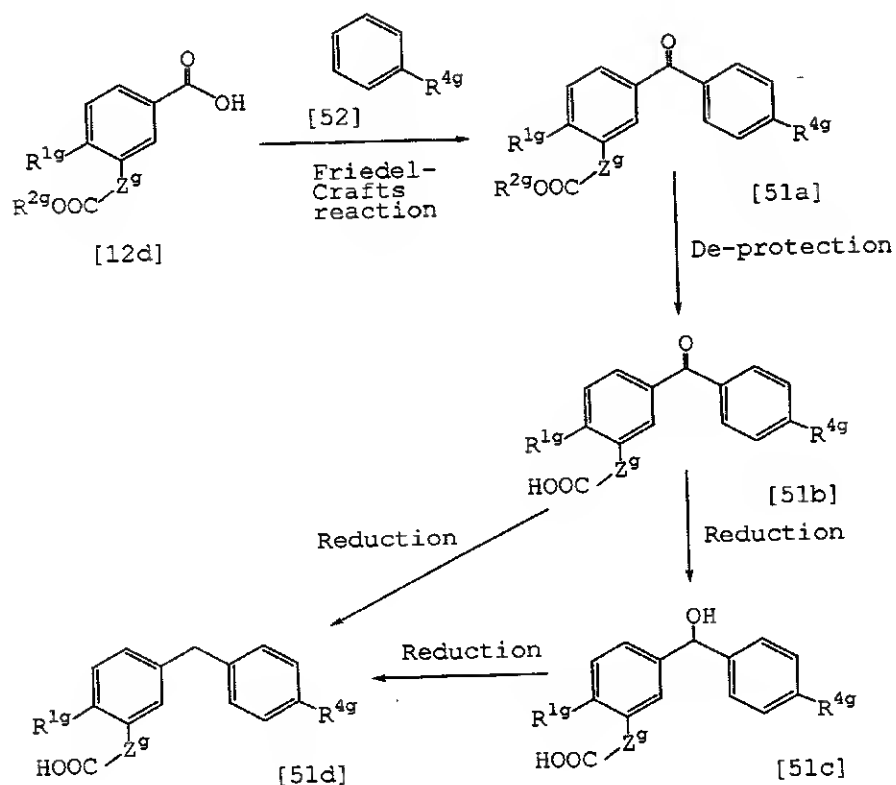
formula [46a] is carried out by the same procedure as that for obtaining a compound of general formula [30b] from a compound of general formula [30a] in Production Process 10.

- 5 The reaction for obtaining a compound of general formula [46c] from a compound of general formula [46b] is carried out by the same procedure as that for obtaining a compound of general formula [30c] from a compound of general formula [30b] in Production
- 10 Process 10.

- The reaction for obtaining a compound of general formula [46d] from compounds of general formulas [46b] and [46c] is carried out by the same procedure as that for obtaining a compound of general
- 15 formula [30d] from compounds of general formulas [30b] and [30c] in Production Process 10.

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[Production Process 20]



wherein R^{1g} , R^{2g} (hydrogen atom is excepted), R^{4g} and Z^g are as defined above.

The reaction for obtaining a compound of general formula [51a] from a compound of general formula [12d] is carried out by the same procedure as that for obtaining a compound of general formula [3a] from a compound of general formula [12] in Production Process 2.

The reaction for obtaining a compound of general formula [51b] from a compound of general formula [51a] is carried out by the same procedure as

that for obtaining a compound of general formula [3b] from a compound of general formula [3a] in Production Process 2.

The reaction for obtaining a compound of
5 general formula [51c] from a compound of general formula [51b] is carried out by the same procedure as that for obtaining a compound of general formula [3c] from a compound of general formula [3b] in Production Process 2.

10 The reaction for obtaining a compound of general formula [51d] from compounds of general formulas [51b] and [51c] is carried out by the same procedure as that for obtaining a compound of general formula [3d] from compounds of general formulas [3b]
15 and [3c] in Production Process 2.

Among the compounds used in the above-mentioned production processes, those which can take a form of salt can be used as a salt. Examples of such salt include the same salts as mentioned in the
20 paragraphs describing the compounds conforming to the pharmacophore of formula 1 and compounds of general formulas [2], [2b], [3], [4], [5], [a], [b], [c], [d], [e], [f] and [g].

Some of the compounds used in the above-
25 mentioned production processes may have isomers such as optical isomers, geometric isomers and tautomers. In such cases, the isomers are also usable. In cases where solvated products, hydrates and various crystal

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Some of the compounds used in the above-mentioned production processes have a substituent which can

group, carboxyl group and the like. When such a compound is used, it is also possible to protect these groups with conventional protecting group previously, and after the reaction, to eliminate these protecting groups by methods which are well known in themselves.

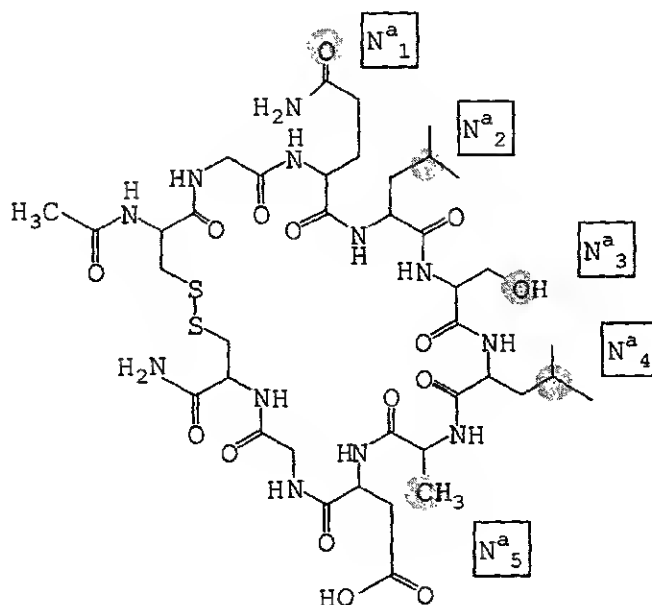
as a medical drug. adjuvants conventionally used for making a preparation such as excipient, carrier, diluent and the like may be incorporated appropriately.

can be administered in the usual manner either orally or non-orally in the form of tablet, capsule, powder, syrup, granule, pill, suspension, emulsion, solution, powdery preparation, suppository, ointment, injection, etc. The method of administration, the dosage and the frequency of administration can be properly selected in accordance with age, body weight and symptoms of the patient. To adult patients, the compound of this invention is given orally or non-orally (for example, by injection, drip infusion, intrarectal administration, etc., at a dosage of 0.1 to 100 mg/kg/day in one portion or several portions.

Next, conformity of typical compounds of this

invention to pharmacophore will be mentioned. In the tables presented below, the unit of distance is angstrom.

For example, in a cyclic peptide of Example 3
 5 (5) represented by the following formula:



wherein the framed letters N^a_1 , N^a_2 , N^a_3 , N^a_4 and N^a_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^a_1 , N^a_2 , N^a_3 , N^a_4 and N^a_5 have the
 10 characters shown in the following Table 38, and there exists a local minimum structure in which the interatomic distances are as shown in Table 39.

Corresponding
atom

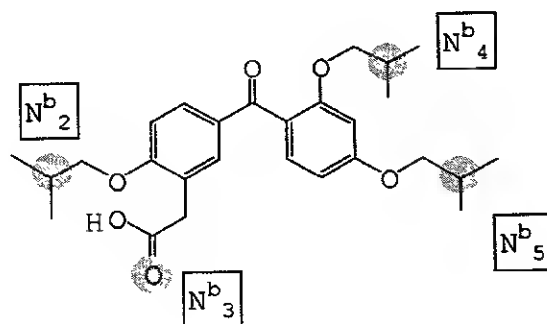
N ^a ₁	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N ^a ₂	Hydrophobic group
N ^a ₃	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N ^a ₄	Hydrophobic group
N ^a ₅	Hydrophobic group

Corresponding
atoms

$N_1^a - N_2^a$	10.23
$N_1^a - N_3^a$	11.89
$N_1^a - N_4^a$	6.69
$N_1^a - N_5^a$	12.21
$N_2^a - N_3^a$	6.35
$N_2^a - N_4^a$	9.73
$N_2^a - N_5^a$	10.54
$N_3^a - N_4^a$	7.75
$N_3^a - N_5^a$	5.31
$N_4^a - N_5^a$	5.85

Accordingly, this compound conforms to a pharmacophore at five atoms.

In the compound of Example 7 represented by the following formula:



- 5 wherein the framed letters N^b_2 , N^b_3 , N^b_4 and N^b_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^b_2 , N^b_3 , N^b_4 and N^b_5 have the characters shown in the following Table 40, and there exists a local minimum
- 10 structure in which the interatomic distances are as shown in Table 41.

[Table 40]

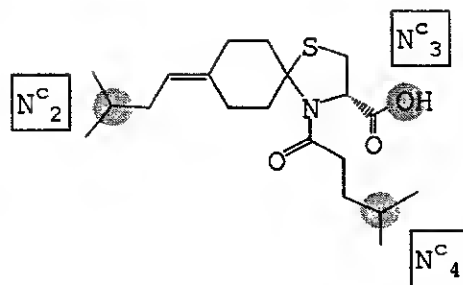
Corresponding atom	Character
N^b_2	Hydrophobic group
N^b_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^b_4	Hydrophobic group
N^b_5	Hydrophobic group

[Table 41]

Corresponding atom	Distance
$N^b_2 - N^b_3$	6.55
$N^b_2 - N^b_4$	10.89
$N^b_2 - N^b_5$	13.10
$N^b_3 - N^b_4$	8.61
$N^b_3 - N^b_5$	7.64
$N^b_4 - N^b_5$	6.59

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 4 represented by
5 the following formula:



wherein the framed letters N^c_2 , N^c_3 and N^c_4 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 and N_4 in formula 1, the N^c_2 , N^c_3 and N^c_4 have the characters shown in the following Table 42, and there exists a locally stabilized structure in which the interatomic distances are as shown in Table 43.

[Table 42]

Corresponding atom	Character
N^c_2	Hydrophobic group
N^c_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^c_4	Hydrophobic group

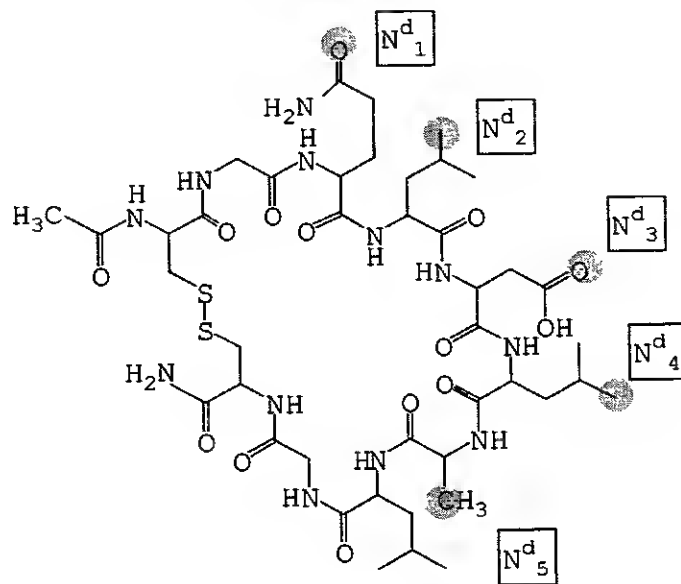
[Table 43]

Corresponding atoms	Distance
------------------------	----------

$N^c_2 - N^c_3$	9.07
$N^c_2 - N^c_4$	10.08
$N^c_3 - N^c_4$	4.85

Accordingly, this compound conforms to a pharmacophore at three atoms.

In the cyclic peptide of Example 3 (1) represented by the following formula:



wherein the framed letters N_1^d , N_2^d , N_3^d , N_4^d and N_5^d represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N_1^d , N_2^d , N_3^d , N_4^d and N_5^d have the

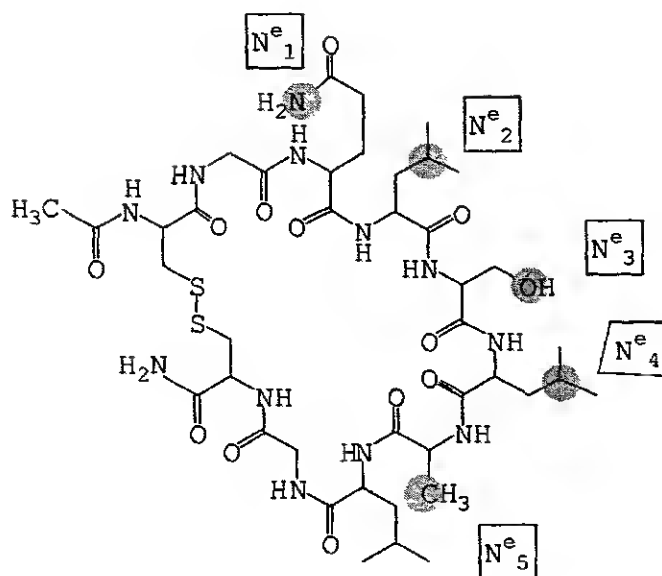
5 characters shown in the following Table 44, and there exists a local minimum structure in which the atomic distances are as shown in Table 45.

[Table 44]

Corresponding atom	Character
N_1^d	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_2^d	Hydrophobic group
N_3^d	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^d	Hydrophobic group
N_5^d	Hydrophobic group

Corresponding atoms	Distance
$N_1^d - N_2^d$	10.23
$N_1^d - N_3^d$	10.24
$N_1^d - N_4^d$	3.63
$N_1^d - N_5^d$	9.03
$N_2^d - N_3^d$	5.97
$N_2^d - N_4^d$	11.84
$N_2^d - N_5^d$	12.23
$N_3^d - N_4^d$	9.90
$N_3^d - N_5^d$	7.86
$N_4^d - N_5^d$	6.18

In the cyclic peptide of Example 3 (2)
represented by the following formula:



wherein the framed letters N^e_1 , N^e_2 , N^e_3 , N^e_4 and N^e_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^e_1 , N^e_2 , N^e_3 , N^e_4 and N^e_5 have the characters shown in the following Table 46, and there exists a local minimum structure in which the interatomic distances are as shown in Table 47.

[Table 46]

Corresponding atom	Character
N^e_1	The atom to which the donative hydrogen atom in the hydrogen-bond donating group is bonded
N^e_2	Hydrophobic group
N^e_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^e_4	Hydrophobic group
N^e_5	Hydrophobic group

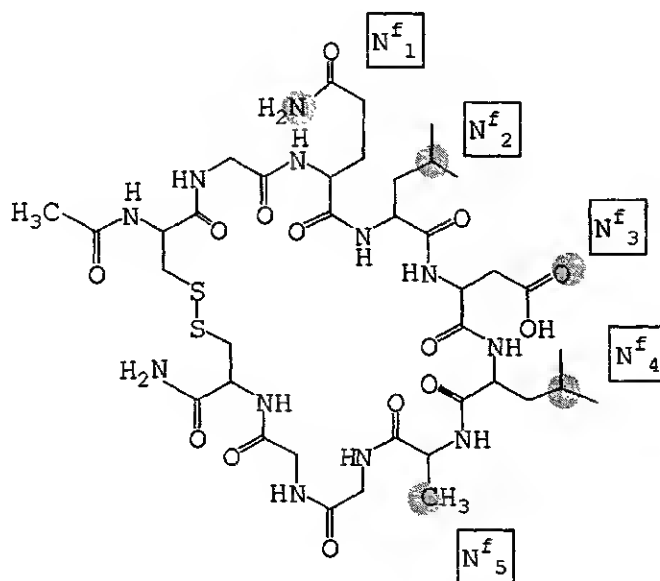
[Table 47]

Corresponding atoms	Distance
$N^e_1 - N^e_2$	7.72
$N^e_1 - N^e_3$	12.14
$N^e_1 - N^e_4$	9.41
$N^e_1 - N^e_5$	15.29
$N^e_2 - N^e_3$	7.61
$N^e_2 - N^e_4$	9.29
$N^e_2 - N^e_5$	11.00
$N^e_3 - N^e_4$	6.18
$N^e_3 - N^e_5$	3.65
$N^e_4 - N^e_5$	7.54

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Accordingly, this compound conforms to a pharmacophore at five atoms.

In the cyclic peptide of Example 3 (3) represented by the following formula:



- 5 wherein the framed letters N^f_1 , N^f_2 , N^f_3 , N^f_4 and N^f_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^f_1 , N^f_2 , N^f_3 , N^f_4 and N^f_5 have the characters shown in the following Table 48, and there
- 10 exists a local minimum structure in which the interatomic distances are as shown in Table 49.

[Table 48]

Corresponding atom	Character
N_1^f	The atom to which the donative hydrogen atom in the hydrogen-bond donating group is bonded
N_2^f	Hydrophobic group
N_3^f	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^f	Hydrophobic group
N_5^f	Hydrophobic group

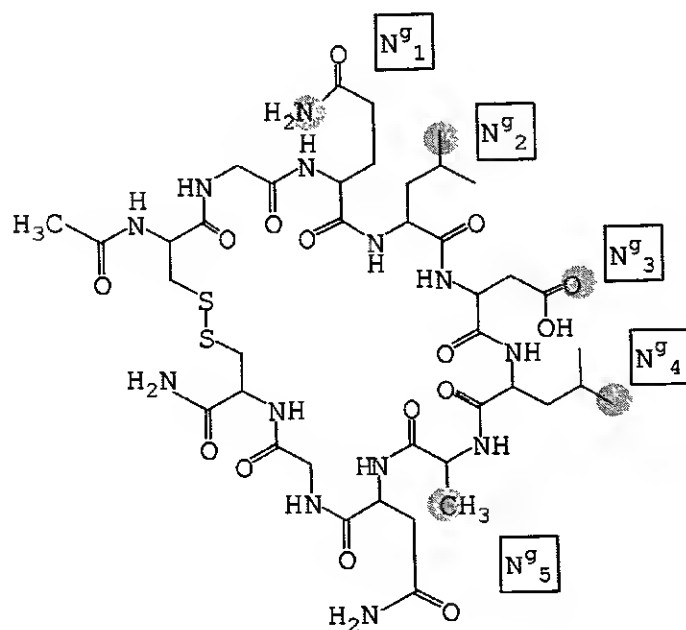
[Table 49]

Corresponding atoms	Distance
$N_1^f - N_2^f$	8.44
$N_1^f - N_3^f$	13.51
$N_1^f - N_4^f$	9.76
$N_1^f - N_5^f$	14.87
$N_2^f - N_3^f$	8.46
$N_2^f - N_4^f$	9.77
$N_2^f - N_5^f$	11.20
$N_3^f - N_4^f$	6.66
$N_3^f - N_5^f$	5.17
$N_4^f - N_5^f$	7.13

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Accordingly, this compound conforms to a pharmacophore at five atoms.

In the cyclic peptide of Example 3 (4) represented by the following formula:



- 5 wherein the framed letters N^g_1 , N^g_2 , N^g_3 , N^g_4 and N^g_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^g_1 , N^g_2 , N^g_3 , N^g_4 and N^g_5 have the characters shown in the following Table 50, and there
- 10 exists a local minimum structure in which the interatomic distances are as shown in Table 51.

[Table 50]

Correspond- ing atom	Character
N^g_1	The atom to which the donative hydrogen atom in the hydrogen-bond donating group is bonded
N^g_2	Hydrophobic group
N^g_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^g_4	Hydrophobic group
N^g_5	Hydrophobic group

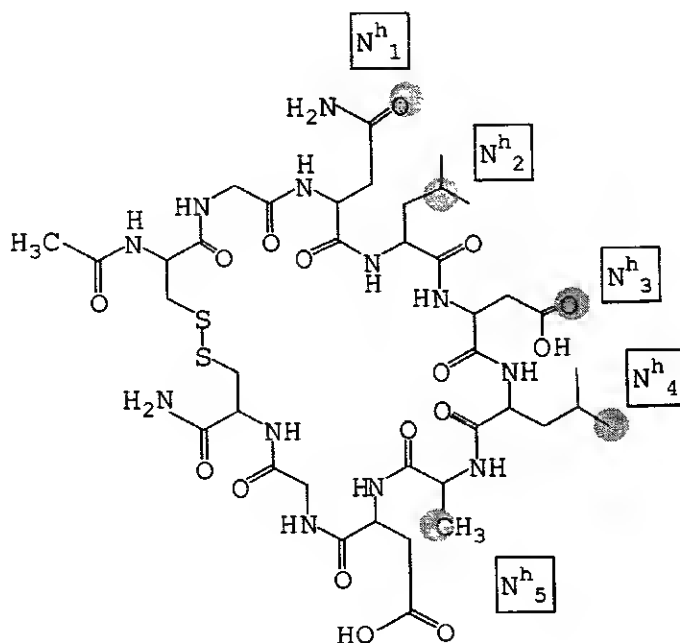
[Table 51]

Corresponding atoms	Distance
$N^g_1 - N^g_2$	11.24
$N^g_1 - N^g_3$	13.23
$N^g_1 - N^g_4$	12.01
$N^g_1 - N^g_5$	14.86
$N^g_2 - N^g_3$	4.35
$N^g_2 - N^g_4$	11.87
$N^g_2 - N^g_5$	10.66
$N^g_3 - N^g_4$	9.39
$N^g_3 - N^g_5$	7.09
$N^g_4 - N^g_5$	6.59

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Accordingly, this compound conforms to a pharmacophore at five atoms.

In the cyclic peptide of Example 3 (6) represented by the following formula:



- 5 wherein the framed letters N^h_1 , N^h_2 , N^h_3 , N^h_4 and N^h_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^h_1 , N^h_2 , N^h_3 , N^h_4 and N^h_5 have the characters shown in the following Table 52, and there
- 10 exists a local minimum structure in which the interatomic distances are as shown in Table 53.

[Table 52]

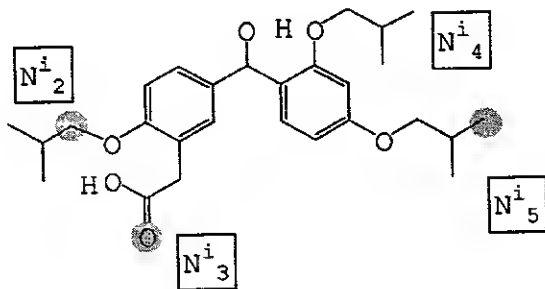
Correspond- ing atom	Character
N^h_1	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^h_2	Hydrophobic group
N^h_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^h_4	Hydrophobic group
N^h_5	Hydrophobic group

[Table 53]

Corresponding atoms	Distance
$N^h_1 - N^h_2$	5.63
$N^h_1 - N^h_3$	9.79
$N^h_1 - N^h_4$	8.79
$N^h_1 - N^h_5$	13.51
$N^h_2 - N^h_3$	8.26
$N^h_2 - N^h_4$	9.19
$N^h_2 - N^h_5$	11.29
$N^h_3 - N^h_4$	6.95
$N^h_3 - N^h_5$	4.27
$N^h_4 - N^h_5$	8.07

Accordingly, this compound conforms to a pharmacophore at five atoms.

In the compound of Example 9 represented by the following formula:



- 5 wherein the framed letters N^i_2 , N^i_3 , N^i_4 and N^i_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^i_2 , N^i_3 , N^i_4 and N^i_5 have the characters shown in the following Table 54, and there exists a local minimum
- 10 structure in which the interatomic distances are as shown in Table 55.

[Table 54]

Corresponding atom	Character
N^i_2	Hydrophobic group
N^i_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^i_4	Hydrophobic group
N^i_5	Hydrophobic group

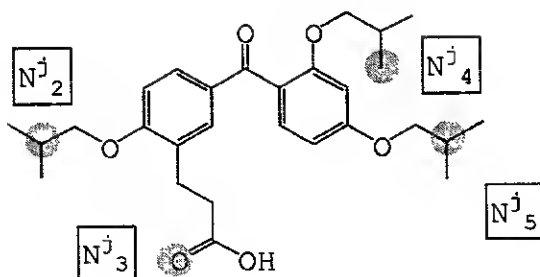
[Table 55]

Corresponding atoms	Distance
$N^i_2 - N^i_3$	4.44
$N^i_2 - N^i_4$	6.97
$N^i_2 - N^i_5$	13.22
$N^i_3 - N^i_4$	5.19
$N^i_3 - N^i_5$	9.74
$N^i_4 - N^i_5$	7.06

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 12 represented by the following formula:

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wherein the framed letters N^j_2 , N^j_3 , N^j_4 and N^j_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^j_2 , N^j_3 , N^j_4 and N^j_5 have the characters shown in the

5 following Table 56, and there exists a local minimum structure in which the interatomic distances are as shown in Table 57.

[Table 56]

Corresponding
atom

Character

 N^j_2

Hydrophobic group

N^j_3

Hydrogen-bond accepting atom in the
hydrogen-bond accepting group

N^j_4

Hydrophobic group

N^j_5

Hydrophobic group

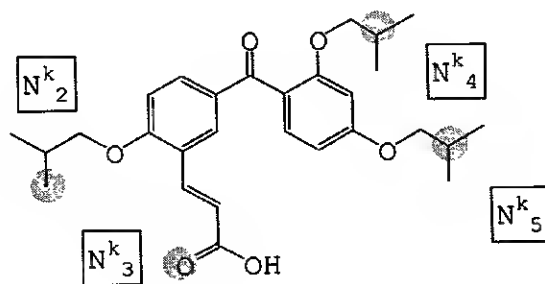
[Table 57]

Corresponding atoms	Distance
------------------------	----------

$N^j_2 - N^j_3$	3.87
$N^j_2 - N^j_4$	8.33
$N^j_2 - N^j_5$	9.42
$N^j_3 - N^j_4$	8.12
$N^j_3 - N^j_5$	9.45
$N^j_4 - N^j_5$	4.80

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 13 represented by the following formula:



- 5 wherein the framed letters N^k_2 , N^k_3 , N^k_4 and N^k_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^k_2 , N^k_3 , N^k_4 and N^k_5 have the characters shown in the

following Table 58, and there exists a local minimum structure in which the interatomic distances are as shown in Table 59.

[Table 58]

Corresponding atom	Character
N_2^k	Hydrophobic group
N_3^k	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^k	Hydrophobic group
N_5^k	Hydrophobic group

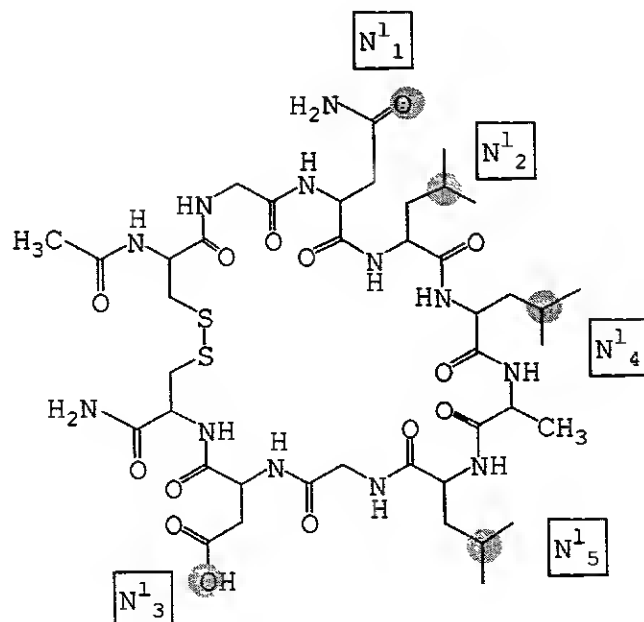
[Table 59]

Corresponding atoms	Distance
$N_2^k - N_3^k$	7.63
$N_2^k - N_4^k$	13.26
$N_2^k - N_5^k$	13.28
$N_3^k - N_4^k$	10.39
$N_3^k - N_5^k$	9.48
$N_4^k - N_5^k$	7.68

Accordingly, this compound conforms to a
5 pharmacophore at four atoms.

In the cyclic peptide of Example 3 (10)

represented by the following formula:



wherein the framed letters N^1_1 , N^1_2 , N^1_3 , N^1_4 and N^1_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_1 , N_2 , N_3 , N_4 and N_5 in formula 1, the N^1_1 , N^1_2 , N^1_3 , N^1_4 and N^1_5 have the characters shown in the following Table 60, and there exists a local minimum structure in which the interatomic distances are as shown in Table 61.

[Table 60]

Correspond- ing atom	Character
N^1_1	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^1_2	Hydrophobic group
N^1_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^1_4	Hydrophobic group
N^1_5	Hydrophobic group

[Table 61]

Corresponding atoms	Distance
$N^1_1 - N^1_2$	5.33
$N^1_1 - N^1_3$	12.02
$N^1_1 - N^1_4$	8.40
$N^1_1 - N^1_5$	12.16
$N^1_2 - N^1_3$	9.33
$N^1_2 - N^1_4$	8.42
$N^1_2 - N^1_5$	10.53
$N^1_3 - N^1_4$	8.88
$N^1_3 - N^1_5$	7.77
$N^1_4 - N^1_5$	4.36

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[Table 62]

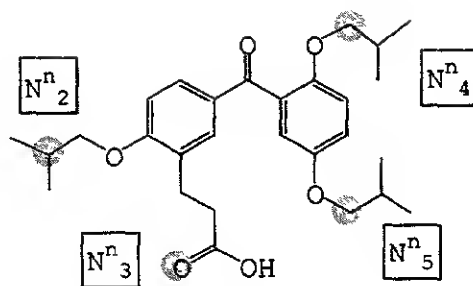
Corresponding atom	Character
N^m_2	Hydrophobic group
N^m_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^m_4	Hydrophobic group
N^m_5	Hydrophobic group

[Table 63]

Corresponding atoms	Distance
$N^m_2 - N^m_3$	6.51
$N^m_2 - N^m_4$	12.58
$N^m_2 - N^m_5$	12.01
$N^m_3 - N^m_4$	9.00
$N^m_3 - N^m_5$	5.85
$N^m_4 - N^m_5$	6.47

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 43 represented by the following formula:



5

Corresponding atom	Character

N_2^n	Hydrophobic group
N_3^n	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^n	Hydrophobic group
N_5^n	Hydrophobic group

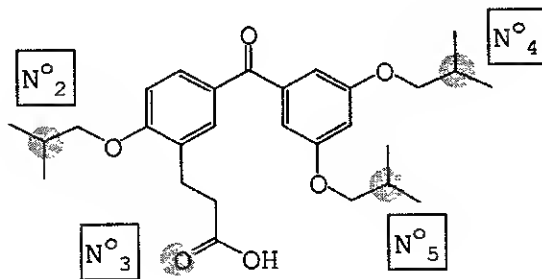
[Table 65]

Corresponding atoms	Distance
------------------------	----------

$N_2^n - N_3^n$	8.37
$N_2^n - N_4^n$	8.72
$N_2^n - N_5^n$	12.02
$N_3^n - N_4^n$	6.80
$N_3^n - N_5^n$	5.39
$N_4^n - N_5^n$	7.43

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 41 represented by the following formula:



- 5 wherein the framed letters N_2° , N_3° , N_4° and N_5° represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N_2° , N_3° , N_4° and N_5° have the characters shown in the

following Table 66, and there exists a local minimum structure in which the interatomic distances are as shown in Table 67.

[Table 66]

Corresponding atom	Character
N ^o ₂	Hydrophobic group
N ^o ₃	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N ^o ₄	Hydrophobic group
N ^o ₅	Hydrophobic group

[Table 67]

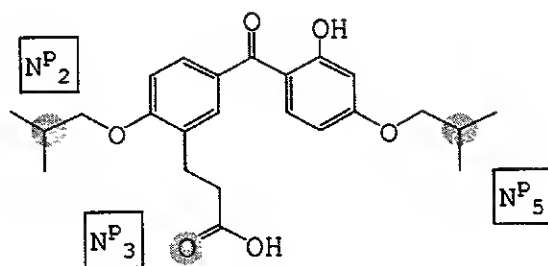
Corresponding atoms	Distance
N ^o ₂ - N ^o ₃	8.29
N ^o ₂ - N ^o ₄	8.47
N ^o ₂ - N ^o ₅	12.68
N ^o ₃ - N ^o ₄	5.66
N ^o ₃ - N ^o ₅	6.43
N ^o ₄ - N ^o ₅	8.08

Accordingly, this compound conforms to a
5 pharmacophore at four atoms.

In the compound of Example 38 represented by

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the following formula:



wherein the framed letters N_2^P , N_3^P and N_5^P represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 and N_5 in formula 1, the N_2^P , N_3^P and N_5^P have the characters shown in the following Table 68, and there exists a local minimum structure in which the interatomic distances are as shown in Table 69.

[Table 68]

10	Corresponding atom	Character

	N^P_2	Hydrophobic group
	N^P_3	Hydrogen-bond accepting atom in the
15		hydrogen-bond accepting group
	N^P_5	Hydrophobic group

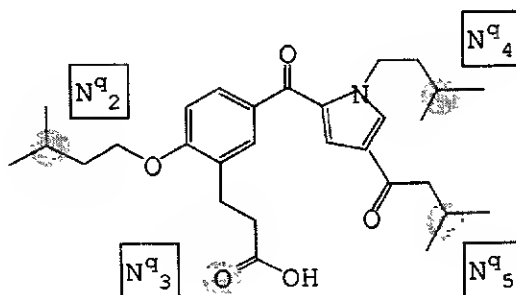
[Table 69]

Corresponding atoms	Distance
------------------------	----------

$N^P_2 - N^P_3$	6.26
$N^P_2 - N^P_5$	12.96
$N^P_3 - N^P_5$	6.97

Accordingly, this compound conforms to a pharmacophore at three atoms.

In the compound of Example 88 represented by the following formula:



- 5 wherein the framed letters N^q_2 , N^q_3 , N^q_4 and N^q_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^q_2 , N^q_3 , N^q_4 and N^q_5 have the characters shown in the following Table 70, and there exists a local minimum
- 10 structure in which the interatomic distances are as shown in Table 71.

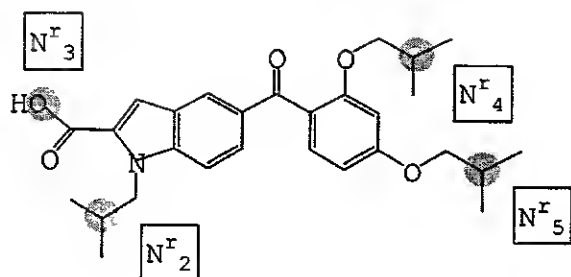
Corresponding
atom

N_2^q	Hydrophobic group
N_3^q	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^q	Hydrophobic group
N_5^q	Hydrophobic group

Corresponding
atoms

$N_2^q - N_3^q$	6.15
$N_2^q - N_4^q$	10.68
$N_2^q - N_5^q$	11.31
$N_3^q - N_4^q$	7.84
$N_3^q - N_5^q$	9.12
$N_4^q - N_5^q$	8.15

In the compound of Example 82 represented by the following formula:



wherein the framed letters N^r_2 , N^r_3 , N^r_4 and N^r_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^r_2 , N^r_3 , N^r_4 and N^r_5 have the characters shown in the

5 following Table 72, and there exists a local minimum structure in which the interatomic distances are as shown in Table 73.

[Table 72]

Corresponding
atom

Character

N^r_2	Hydrophobic group
N^r_3	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N^r_4	Hydrophobic group
N^r_5	Hydrophobic group

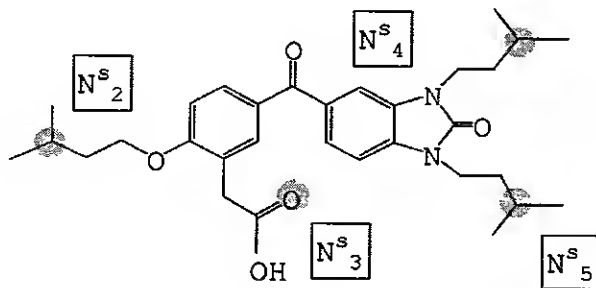
[Table 73]

Corresponding atoms	Distance
------------------------	----------

$N^r_2 - N^r_3$	5.41
$N^r_2 - N^r_4$	8.10
$N^r_2 - N^r_5$	12.32
$N^r_3 - N^r_4$	6.45
$N^r_3 - N^r_5$	9.56
$N^r_4 - N^r_5$	5.58

Accordingly, this compound conforms to a pharmacophore at four atoms.

In the compound of Example 90 represented by the following formula:



- 5 wherein the framed letters N^s_2 , N^s_3 , N^s_4 and N^s_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 , N_4 and N_5 in formula 1, the N^s_2 , N^s_3 , N^s_4 and N^s_5 have the characters shown in the

following Table 74, and there exists a local minimum structure in which the interatomic distances are as shown in Table 75.

[Table 74]

Corresponding atom	Character
N_2^s	Hydrophobic group
N_3^s	Hydrogen-bond accepting atom in the hydrogen-bond accepting group
N_4^s	Hydrophobic group
N_5^s	Hydrophobic group

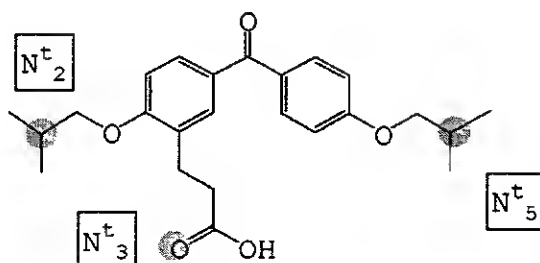
[Table 75]

Corresponding atoms	Distance
$N_2^s - N_3^s$	5.11
$N_2^s - N_4^s$	13.14
$N_2^s - N_5^s$	10.85
$N_3^s - N_4^s$	8.81
$N_3^s - N_5^s$	5.95
$N_4^s - N_5^s$	5.59

Accordingly, this compound conforms to a
5 pharmacophore at four atoms.

In the compound of Example 25(8) represented

by the following formula:



wherein the framed letters N^t_2 , N^t_3 and N^t_5 represent the shaded atoms, respectively, to signify the atoms corresponding to N_2 , N_3 and N_5 in formula 1, the N^t_2 , N^t_3 and N^t_5 have the characters shown in the following Table 76, and there exists a local minimum structure in which the interatomic distances are as shown in Table 77.

[Table 76]

Corresponding
atom

Character

N^t_2

Hydrophobic group

N^t_3

Hydrogen-bond accepting atom in the
hydrogen-bond accepting group

N^t_5

Hydrophobic group

Corresponding atoms	Distance
------------------------	----------

$N_2^t - N_3^t$	5.83
$N_2^t - N_5^t$	13.01
$N_3^t - N_5^t$	7.79

Next, pharmacological activities of typical compounds of this invention will be described.

Test Example 1: Activities on AP-1 binding reaction to recognition sequence (ELISA)

Nuclear extract protein containing transcription factor AP-1 prepared from HeLa cells was coated on 96-well ELISA plate (100 ng/well) in Hepes buffer (20 mM Hepes-potassium hydroxide (pH 7.9), 0,5 mM ethylenediamine-tetraacetic acid, 50 mM potassium chloride, 10% glycerol). After washing, a blocking treatment was carried out with bovine serum albumin, and then used for a binding assay using nuclear extract protein.

On the other hand, Jun peptide and N-terminal biotinylated tetraglycine Fos peptide containing a DNA-binding site [Nature, Vol. 373, Pages 257-261, 1995]

were synthesized and separately dissolved in tris buffer (20 mM tris-hydrochloride (pH 7.5), 50 mM potassium chloride, 1 mM ethylenediaminetetraacetic acid, 10 mM magnesium chloride, 1 mM dithiothreitol, 5 0.5M guanidine hydrochloride, 30% glycerol). Equimolar quantities of both the solutions were mixed together, and the mixture was used as an AP-1 complex (Fos/Jun peptide). The AP-1 complex was added to avidin-coating 96-well ELISA plate (10 pmol/well), washed, and then 10 blocked with bovine serum albumin. The product was used for binding assay using AP-1 complex.

On the basis of the above-mentioned two coated AP-1, a digoxigenin-labeled double stranded oligonucleotide (22-mer) containing an AP-1 binding 15 sequence (3'-TGAGTCA-5') which has been synthesized elsewhere was reacted in the presence and absence of a sample at room temperature for 30-60 minutes in a binding reaction solution [Hepes buffer or 25 mM tris-hydrochloric acid (pH 7.9), 0.5 mM 20 ethylenediaminetetraacetic acid, 0.05% Nonidet P-40, 10% glycerol]. After of the reaction, unbound labeled oligonucleotide was washed out with Hepes buffer solution containing 0.05% of Tween-20. Then, an anti-digoxigenin antibody labeled with peroxidase was added, 25 and reacted with the labeled oligonucleotide bound to AP-1. After washing out the excessive antibody with Hepes buffer containing 0.05% of Tween-20, the residue was reacted for a predetermined period of time in a 100

5

.79.

10

Table 78 Results on ELISA using Fos/Jun peptide

Example No.	Inhibition rate %	
	200 μ M	500 μ M
4	8	15
7	14	46
8	9	20
9	23	37
12	24	90
13	43	96
14	21	90
15	19	64
16	21	65
25 (5)	39	98
25 (8)	27	79
37 (7)	4	22
38	18	91
41	27	78
43	28	72
47	35	92
53	30	79
57	13	62
58	22	88
68 (2)	78	96
68 (8)	24	94
73	18	74
82	28	97
88	29	72
90	26	96

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The samples of Example No. 12, 15, 25(5) and 43 were converted to sodium salts and then measured according to the procedure of Example 17. In Example 68(8), measurement was carried out on the isomer having a lower polarity among the two isomers.

[Table 79]

Table 79 Results on ELISA using nucleus-extracted protein

Example No.	Inhibition rate 100 μ M
2	81
3 (2)	94
3 (3)	43
3 (4)	64
3 (5)	43
3 (6)	42
3 (7)	74
3 (8)	64
3 (9)	48
3 (10)	76
3 (11)	48

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In this test system, compounds exhibiting an inhibition of 10% or more at 500 μ M are preferable when Fos/Jun is used; and compounds exhibiting an inhibition of 10% or more at 100 μ M are preferable when nuclear extract protein is used.

Test Example 2: Type II collagen-induced arthritis in mice

The effect of the compound of Example 12 on the type II collagen-induced arthritis in mice was examined. As the animals, 8 weeks old male DBA/1J mice (Charles River Japan) were used. To 2 mg/mL solution of bovine type II collagen in 0.1 mol/L acetic acid (Kouken) was added an equivalent quantity of Freund complete adjuvant (Nacalai Tesque), and prepared an emulsion. 0.2 ml of the emulsion was subcutaneously injected into the tail root portion. On the 22nd day as counted from the day of first inoculation, the same treatment as above was repeated to induce arthritis. The compound was suspended in 0.5% methyl cellulose solution and administered orally at 100 mg/kg once every day from the 22nd day to the 36th day. To the control group (negative control group), a 0.5% methyl cellulose solution was administered similarly. Severity of the arthritis was evaluated in the following manner:

score 0: no change

score 1: swelling on one or two toes or slight swelling in the foreleg root or hindleg root only;

score 2: swelling and rubor in more joints;

score 3: extensive swelling over whole foreleg or hindleg;

and total of the four legs was calculated. Taking the

5 maximum score as 12, the arthritis score was calculated to evaluate the severity of arthritis. Regarding the destruction of joints and bones, X ray photographs of four paws were taken on the 37th day, and severity of destruction in the second to fifth articulationes

10 interphalangeae, first to fifth articulationes metacarpophalangeae and metatarsophalangeae, and calcaneus was scored by 0 or 1 in accordance with presence or absence of destruction, and the severity of destruction in the carpus and tarsal was scored by 0 to
15 3. Total score for the four paws was taken as joint and bone destruction score, taking 50 points as maximum score.

The results on the 37th day from the first inoculation was as follows:

20 Control group: arthritis score 8, joint and bone destruction score 26;

Compound-administered group: arthritis score 3, joint and bone destruction score 10.

That is, the inhibition rate as compared with
25 control group was 63% and 62%, respectively.

BEST MODE FOR CARRYING OUT THE INVENTION

Next, this invention is explained by

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referring to examples. The invention is by no means limited by these examples.

For expression of amino acid residue, the 3-letters expression system prescribed by IUPAC and IUB is used. Unless otherwise defined, an amino acid means L-form. The abbreviations have the following meanings:

Fmoc: 9-fluorenylmethoxycarbonyl

PyBOP: benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate

10 HOBt: N-hydroxybenzotriazole monohydrate

DMF: N,N-dimethylformamide

DIEA: N,N-diisopropylethylamine

DCM: dichloromethane

TFA: trifluoroacetic acid

15 DMSO: dimethyl sulfoxide

Cys(Trt): S-trityl-L-cysteine

Asp(tBu): β -tert-butyl L-aspartate

Ac: acetyl

Me: methyl

20 Et: ethyl

nPr: n-propyl

iPr: isopropyl

iBu: isobutyl

iAm: isoamyl

25 Ph: phenyl

Py: pyridyl

(4-NO₂)PhCH₂: p-nitrobenzyl

CDCl₃: heavy chloroform

093055-150701

d_6 -DMSO: heavy dimethyl sulfoxide

(Cys¹-Cys¹⁰) means that a disulfide linkage is present between the first and 10th Cys residues.

(Cys²-Cys¹¹) means that a disulfide linkage is present
5 between the second and 11th Cys residues.

HPLC purification was carried out under the following conditions:

Column: YMC PROTEIN-RP (250×20 mm I.D.)

Flow rate: 8.0 ml/min.

10 Detection wavelength: UV 230 nm

Mobile phase: CH₃CN (10-30%) in 0.1% TFA-H₂O (30 min.)

As the carrier for silica gel column chromatography, BW-127ZH (manufactured by Fuji Silicia
15 Kagaku) was used.

Example 1

DMF is added to 1.82 g of Rink amide MBHA resin (0.55 mmol/g) to swell the resin. Then, 15 ml of 20% piperidine/DMF solution is added and shaken for 20
20 minutes to remove the Fmoc group. After washing the resin thus obtained with DMF six times, 1.46 g of Fmoc-Cys(Trt)-OH, 0.38 g of HOBT, 1.30 g of PyBOP, 12 ml of DMF and 0.87 ml of DIEA are successively added and shaken for 60 minutes. After filtering off the liquid
25 phase, the resin is washed with DMF six times. By the same procedure as above, amino acid derivatives are successively condensed from the C-terminal side by

successively using Fmoc-Gly-OH, Fmoc-Asp(tBu)-OH, Fmoc-Ala-OH, Fmoc-Leu-OH, Fmoc-Asp(tBu)-OH, Fmoc-Leu-OH, Fmoc-Gln-OH, Fmoc-Gly-OH and Fmoc-Cys(Trt)-OH. After coupling with Fmoc amino acid, the Fmoc groups are removed with piperidine/DMF solution. In 15 ml OF DMF-DCM (1:1) mixture, 0.94 ml of acetic anhydride and 1.74 ml of DIEA are added and shaken for 30 minutes. After filtering off the liquid phase, the resin is washed with DMF four times and with DCM 3 times. Thus, 3.16 g of Ac-Cys(Trt)-Gly-Gln-Leu-Asp(tBu)-Leu-Ala-Asp(tBu)-Gly-Cys(Trt)-Rink amide MBHA resin is obtained.

Example 2

1.42 g of the protected peptide resin obtained in Example 1 is added to 40 ml of 92.5:5:2.5 mixture of TFA-thioanisole-water, and shaken for 4 hours. The insoluble matter is filtered off, and the filtrate is concentrated under reduced pressure. 100 ml of diethyl ether is added to the residue, and the mixture is allowed to stand for 30 minutes at an ice-cooled temperature. After centrifuging the reaction mixture, 100 ml of 10% aqueous acetic acid is added to the residue. After filtering off the insoluble matter, the filtrate is freeze-dried to obtain a powder of straight chain peptide. About 1/4 portion of the straight peptide powder thus obtained is taken and dissolved in 40 ml of 10% DMSO/TFA mixture, and the resulting solution is allowed to stand at ambient

temperature for 15 hours. The reaction mixture is concentrated under reduced pressure, 50 ml of diethyl ether is added, and the mixture thus obtained is allowed to stand for 30 minutes at an ice-cooled temperature. After centrifuging the reaction mixture, 15 ml of 10% aqueous solution of acetic acid is added to the residue, and the insoluble matter is filtered off. The filtrate thus obtained is purified by HPLC and freeze-dried to obtain 6 mg of Ac-Cys¹-Gly-Gln-Leu-Asp-Leu-Ala-Asp-Gly-Cys¹⁰-NH₂ (Cys¹-Cys¹⁰).
ESI-MS: m/z 1033 for [M+H]⁺ (calcd. 1032 for C₄₀H₆₄N₁₂O₁₆S₂)

Example 3

The procedure of Example 2 is repeated to obtain the following compounds.

- (3)1 Ac-Cys¹-Gly-Gln-Leu-Asp-Leu-Ala-Leu-Gly-Cys¹⁰-NH₂
(Cys¹-Cys¹⁰)
ESI-MS: m/z 1031 for [M+H]⁺ (calcd 1030 for C₄₂H₇₀N₁₂O₁₄S₂)
- (3)2 Ac-Cys¹-Gly-Gln-Leu-Ser-Leu-Ala-Leu-Gly-Cys¹⁰-NH₂
(Cys¹-Cys¹⁰)
ESI-MS: m/z 1003 for [M+H]⁺ (calcd 1002 for C₄₁H₇₀N₁₂O₁₃S₂)
- 3(3) Ac-Cys¹-Gly-Gln-Leu-Asp-Leu-Ala-Gly-Gly-Cys¹⁰-NH₂
(Cys¹-Cys¹⁰)
ESI-MS: m/z 975 for [M+H]⁺ (calcd 974 for C₃₈H₆₂N₁₂O₁₄S₂)
- 3(4) Ac-Cys¹-Gly-Gln-Leu-Asp-Leu-Ala-Asn-Gly-Cys¹⁰-NH₂
(Cys¹-Cys¹⁰)
ESI-MS: m/z 1032 for [M+H]⁺ (calcd 1031 for C₄₀H₆₅N₁₃O₁₅S₂)
- 3(5) Ac-Cys¹-Gly-Gln-Leu-Ser-Leu-Ala-Asp-Gly-Cys¹⁰-NH₂

(Cys¹-Cys¹⁰)

ESI-MS: m/z 1005 for [M+H]⁺ (calcd 1004 for C₃₉H₆₄N₁₂O₁₅S₂)

3(6) Ac-Cys¹-Gly-Asn-Leu-Asp-Leu-Ala-Asp-Gly-Cys¹⁰-NH₂

(Cys¹-Cys¹⁰)

5 ESI-MS: m/z 1019 for [M+H]⁺ (calcd 1018 for C₃₉H₆₂N₁₂O₁₆S₂)

3(7) Ac-Asn-Cys²-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys¹¹-

NH₂ (Cys²-Cys¹¹)

ESI-MS: m/z 1103 for [M+H]⁺ (calcd 1102 for C₄₄H₇₄N₁₄O₁₅S₂)

3(8) Ac-Cys¹-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Ser-Cys¹⁰-NH₂

10 (Cys¹-Cys¹⁰)

ESI-MS: m/z 989 for [M+H]⁺ (calcd 988 for C₄₀H₆₈N₁₂O₁₃S₂)

3(9) Ac-Asn-Cys²-Gly-Asn-Ala-Leu-Ala-Leu-Gly-Ser-Cys¹¹-

NH₂ (Cys²-Cys¹¹)

ESI-MS: m/z 1061 for [M+H]⁺ (calcd 1060 for C₄₁H₆₈N₁₄O₁₅S₂)

15 3(10) Ac-Cys¹-Gly-Asn-Leu-Leu-Ala-Leu-Gly-Asp-Cys¹⁰-NH₂

(Cys¹-Cys¹⁰)

ESI-MS: m/z 1017 for [M+H]⁺ (calcd 1016 for C₄₁H₆₈N₁₂O₁₄S₂)

3(11) Ac-Cys¹-Gly-Asn-Leu-Leu-Ser-Leu-Gly-Asp-Cys¹⁰-NH₂

(Cys¹-Cys¹⁰)

20 ESI-MS: m/z 1033 for [M+H]⁺ (calcd 1032 for C₄₁H₆₈N₁₂O₁₅S₂)

Example 4

In 8 ml of methylene chloride are dissolved
0.79 g of (3S)-8-(3-methylbutylidene)-1-thia-4-
azaspiro[4.5]decane-3-carboxylic acid and 1.20 ml of
25 triethylamine. Into the solution thus obtained are
dropwise added a solution of isocaproyl chloride
(prepared from 0.48 ml of isocaproic acid, 0.38 ml of

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oxalyl chloride and 5 ml of methylene chloride) in methylene chloride at 5-10°C, and stirred at ambient temperature for 2 hours. The whole was acidified to pH 2.0 with 2 mol/L HCl and extracted with CHCl₃. The combined organic extracts were washed with water and brine, dried on MgSO₄ and concentrated under reduced pressure. The residue was purified by chromatography, [eluent; chloroform:methanol = 9:1] to obtain 1.10 g of (3S)-8-(3-methylbutylidene)-4-(4-methylpentanoyl)-1-thia-4-azaspiro[4.5]-decane-3-carboxylic acid as a colorless crystalline product.

NMR (CDCl₃) δ: 0.7-1.1 (12H,m), 1.2-3.4 (18H,m), 4.8-5.3 (2H,m), 6.9-7.4 (1H,bs)

Example 5

In 6 ml of methylene chloride is dissolved 0.62 g of 4-isobutoxy-3-(2-methoxy-2-oxoethyl)benzoic acid. After adding 0.25 ml of oxalyl chloride at ambient temperature, the mixture thus obtained is stirred at ambient temperature for one hour. Then, 0.62 g of aluminum chloride and 0.77 g of 1,3-diisobutoxybenzene are successively added at 5-10°C, and the mixture is stirred at ambient temperature for one hour. The reaction mixture is added to a mixture of chloroform and water, and the organic layer is separated. The organic layer is successively washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate,

and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography [eluent; n-hexane:ethyl acetate = 95:5] to obtain 0.63 g of methyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetate as a colorless oily product.

NMR (CDCl₃) δ: 0.73 (6H,d,J=6.6Hz), 1.02 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.6Hz), 1.5-2.4 (3H,m), 3.5-4.0 (11H,m), 6.4-6.7 (2H,m), 6.81 (1H,d,J=8.1Hz), 7.35 (1H,d,J=8.5Hz), 7.5-7.9 (2H,m)

Example 6

The procedure of Example 5 is repeated to obtain isobutyl 5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoate.

NMR (CDCl₃) δ: 0.69 (6H,d,J=6.6Hz), 0.9-1.2 (18H,m), 1.2-2.4 (4H,m), 3.63 (2H,d,J=6.3Hz), 3.77 (2H,d,J=6.6Hz), 3.85 (2H,d,J=7.6Hz), 4.06 (2H,d,J=6.6Hz), 6.3-6.7 (2H,m), 6.95 (1H,d,J=8.8Hz), 7.40 (1H,d,J=8.1Hz), 7.94 (1H,dd,J=8.7,2.4Hz), 8.17 (1H,d,J=2.4Hz)

Example 7

In 6 ml of methanol is dissolved 0.57 g of methyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetate. After adding 0.72 ml of 5 mol/L solution of sodium hydroxide, the mixture thus obtained is stirred at ambient temperature for one hour

and thereafter at 50-60°C for one hour. Chloroform and water are added to the reaction mixture, pH is adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is successively
5 washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 0.45 g of 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetic acid is
10 obtained as a colorless crystalline product.
NMR (CDCl₃) δ: 0.7-1.1 (18H,m), 1.5-2.3 (3H,m), 3.6-3.9 (8H,m), 6.4-7.8 (7H,m)

Example 8

The procedure of Example 7 is repeated to
15 obtain 5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoic acid.

NMR (CDCl₃) δ: 0.65 (6H,d,J=6.8Hz), 0.9-1.2 (12H,m), 1.2-2.4 (3H,m), 3.62 (2H,d,J=6.4Hz), 3.78 (2H,d,J=6.6Hz), 4.10 (2H,d,J=6.4Hz), 6.4-6.6 (2H,m), 7.0-8.6 (1H,bs),
20 7.09 (1H,d,J=8.8Hz), 7.44 (1H,d,J=8.5Hz), 8.11 (1H,dd,J=8.8,2.2Hz), 8.47 (1H,d,J=2.2Hz)

Example 9

In 2 ml of methanol is dissolved 100 mg of 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetic
25 acid. After adding 18 mg of sodium borohydride at 5-10°C, the mixture thus obtained is stirred at 50-60°C

for one hour. Then, 40 mg of sodium borohydride and 40 mg of lithium chloride are further added at ambient temperature, and the mixture thus obtained is stirred at 50-60°C for two hours. Chloroform and water are added to the reaction mixture, pH is adjusted to 2.0 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is successively washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 50 mg of 2-{5-[(2,4-diisobutoxyphenyl)(hydroxy)methyl]-2-isobutoxyphenyl}-acetic acid is obtained as a colorless oily product. NMR (CDCl₃) δ: 0.7-1.1 (18H,m), 1.5-2.3 (3H,m), 3.4-3.9 (10H,m), 5.93 (1H,s), 5.7-7.5 (6H,m)

Example 10

The procedure of Example 5 is repeated to obtain ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]propionate.

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.8Hz), 1.0-1.1 (12H,m), 1.23 (3H,t,J=7.1Hz), 1.5-2.3 (3H,m), 2.4-2.7 (2H,m), 2.8-3.1 (2H,m), 3.6-3.8 (6H,m), 4.12 (2H,q,J=6.8Hz), 6.4-6.6 (2H,m), 6.78 (1H,d,J=9.3Hz), 7.2-7.4 (1H,m), 7.5-7.7 (2H,m)

Example 11

The procedure of Example 5 is repeated to

obtain ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-2-propenoate.

NMR (CDCl₃) δ : 0.68 (6H,d,J=6.6Hz), 1.01 (6H,d,J=6.3Hz),
1.07 (6H,d,J=6.1Hz), 1.33 (3H,t,J=7.1Hz), 1.6-2.4
5 (3H,m), 3.6-3.9 (6H,m), 4.25 (2H,q,J=7.1Hz), 6.3-8.1
(8H,m)

Example 12

The procedure of Example 7 is repeated to
obtain 3-[5-(2,4-diisobutoxybenzoyl)-2-

10 isobutoxyphenyl]propionic acid.

NMR (CDCl₃) δ : 0.70 (6H,d,J=6.8Hz), 1.0-1.1 (12H,m),
1.6-2.4 (3H,m), 2.5-2.8 (2H,m), 2.8-3.1 (2H,m), 3.62
(2H,d,J=6.4Hz), 3.77 (2H,d,J=6.3Hz), 3.80
(2H,d,J=6.1Hz), 6.4-6.6 (2H,m), 6.79 (1H,d,J=9.0Hz),
15 7.2-7.5 (1H,m), 7.6-7.8 (2H,m), 7.8-8.8 (1H,bs)

Example 13

The procedure of Example 7 is repeated to
obtain 3-[5-(2,4-diisobutoxybenzoyl)-2-
isobutoxyphenyl]-2-propenoic acid.

20 NMR CDCl₃ δ : 0.68 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.6Hz),
1.08 (6H,d,J=6.8Hz), 1.5-2.4 (3H,m), 3.63
(2H,d,J=6.3Hz), 3.7-3.9 (4H,m), 6.4-8.2 (9H,m)

Example 14

In 2 ml of tetrahydrofuran is dissolved 150
25 mg of 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-

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2-propenoic acid. After adding 14 mg of lithium aluminum hydride at 5-10°C, the mixture thus obtained is stirred for one hour. The reaction mixture is added to a mixture of chloroform and water, pH is adjusted to 3.0 with 2 mol/L hydrochloric acid, and the organic layer is separated. After successively washing the organic layer with water and saturated aqueous solution of sodium chloride and drying it over anhydrous magnesium sulfate, the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography [eluent; n-hexane:ethyl acetate = 4:1] to obtain 80 mg of 3-[5-[(2,4-diisobutoxyphenyl)(hydroxy)methyl]-2-isobutoxyphenyl]-2-propenoic acid as a colorless foaming product.

NMR (CDCl₃) δ: 0.9-1.1 (18H,m), 1.8-2.4 (3H,m), 3.6-4.0 (7H,m), 5.94 (1H,bs), 6.3-7.7 (8H,m), 8.08 (1H,d,J=16.4Hz)

Example 15

The procedure of Example 14 is repeated to obtain 3-{5-[(2,4-diisobutoxyphenyl)(hydroxy)methyl]-2-isobutoxyphenyl}propionic acid.

NMR (CDCl₃) δ: 0.7-1.1 (18H,m), 1.7-2.3 (3H,m), 2.5-3.1 (4H,m), 3.4-3.9 (7H,m), 5.93 (1H,bs), 6.2-8.0 (7H,m)

Example 16

In 2 ml of ethanol is dissolved 200 mg of 2-

[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetic acid. After adding 40 mg of 5% palladium-carbon, the mixture thus obtained is stirred at ambient temperature for one hour in a stream of hydrogen gas. The reaction mixture is filtered with Celite, and the solvent is distilled off under reduced pressure from the filtrate. The residue thus obtained is purified by silica gel column chromatography [eluent; n-hexane:ethyl acetate = 4:1] to obtain 140 mg of 2-[5-(2,4-diisobutoxybenzyl)-2-isobutoxyphenyl]acetic acid as a colorless oily product.

NMR (CDCl₃) δ: 0.9-1.1 (18H,m), 1.7-2.3(3H,m), 3.4-3.9(10H,m), 6.2-6.5(2H,m), 6.6-7.3(5H,m)

Example 17

In 90 ml of ethanol is dissolved 9.0 g of 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-propionic acid. After adding 18.2 ml of 1 mol/L aqueous solution of sodium hydroxide, the mixture is stirred at ambient temperature for 10 minutes. The solvent is distilled off from the reaction mixture under reduced pressure, and the residue is purified by reverse phase silica gel column chromatography [eluent; acetonitrile:water = 1:1] to obtain 7.6 g of sodium 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-propionate as a colorless foaming product.

NMR (CDCl₃) δ: 0.5-1.1 (18H,m), 1.5-2.5 (5H,m), 2.6-2.9 (2H,m), 3.4-3.9 (6H,m), 6.3-6.7 (3H,m), 7.1-7.5 (2H,m),

7.63 (1H,s)

Example 18

The procedure of Example 17 is repeated to obtain sodium 3-{5-[(2,4-diisobutoxyphenyl)(hydroxy)-methyl]-2-isobutoxyphenyl}propionate.

Example 19

In 4.8 ml of tetrahydrofuran are dissolved 0.16 g of (2R,4R)-4-isobutoxy-2-(4-methylpentyl)pyrrolidine and 0.78 ml of triethylamine, to which is dropwise added a solution of 3-(benzyloxycarbonylmethyl)-4-isobutoxybenzoyl chloride in tetrahydrofuran (prepared from 0.48 g of 3-(benzyloxycarbonylmethyl)-4-isobutoxybenzoic acid, 0.09 ml of oxalyl chloride and 4.8 ml of tetrahydrofuran) at 5-10°C. The mixture thus obtained is stirred at ambient temperature for 15 hours. Ethyl acetate and water are added to the reaction mixture, pH is adjusted to 3.0 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography [eluent; n-hexane:ethyl acetate = 3:1] to obtain 0.18 g of benzyl 2-(2-isobutoxy-5-{[(2R,4R)-4-isobutoxy-2-(4-

methylopentyl)pyrrolidinyl]carbonyl)phenyl)acetate as a yellow-colored oily product.

NMR (CDCl₃) δ: 0.85 (6H,d,J=6.1Hz), 0.89 (6H,d,J=7.6Hz),
1.08 (6H,d,J=7.2Hz), 1.1-2.4 (11H,m), 2.9-3.2 (2H,m),
5 3.5-4.6 (7H,m), 5.12 (2H,bs), 6.82 (1H,d,J=8.3Hz), 7.2-
7.5 (8H,m)

Example 20

The procedure of Example 7 is repeated to
obtain 2-(2-isobutoxy-5-[(2R,4R)-4-isobutoxy-2-(4-
10 methylopentyl)pyrrolidinyl]carbonyl)phenyl)acetic acid.

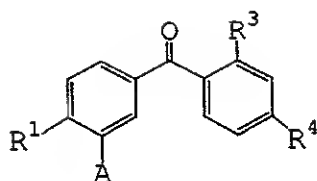
NMR (CDCl₃) δ: 0.8-0.9 (12H,m), 1.02 (6H,d,J=6.6Hz),
1.1-2.4 (11H,m), 2.9-3.2 (2H,m), 3.4-4.0 (7H,m), 4.1-
4.5 (1H,m), 6.81 (1H,d,J=8.6Hz), 7.2-7.6 (3H,m)

Example 21

15 The procedure of Example 5 is repeated to
obtain the compounds shown in Table 80.

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[Table 80]



No.	R ¹	R ³	R ⁴	A
21 (1)	O-iBu	H	O-iBu	CH ₂ COOMe
21 (2)	O-iBu	O-nPr	O-nPr	CH ₂ COOMe
21 (3)	O-iBu	O-iAm	O-iAm	CH ₂ COOMe
21 (4)	O-iAm	O-iBu	O-iBu	CH ₂ COOMe
21 (5)	O-iAm	O-iAm	O-iAm	CH ₂ COOMe
21 (6)	O-iBu	O-iAm	O-iAm	(CH ₂) ₂ COOEt
21 (7)	O-iAm	O-iBu	O-iBu	(CH ₂) ₂ COOEt
21 (8)	O-iBu	H	O-iBu	(CH ₂) ₂ COOEt
21 (9)	O-iAm	O-iAm	O-iAm	(CH ₂) ₂ COOEt
21 (10)	O-iBu	O-iBu	O-iBu	(CH ₂) ₃ COOEt
21 (11)	O-iBu	O-iBu	O-iBu	CH ₂ CH=COOEt
21 (12)	O-iAm	O-iBu	O-iBu	CH ₂ CH=COOEt
21 (13)	O-iAc	O-iBu	O-iBu	(CH ₂) ₂ COOEt

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21(1)

NMR (CDCl₃) δ : 1.05 (12H, d, J=6.6Hz), 1.92-2.28 (2H, m),
3.69 (5H, s), 3.82 (4H, d, J=6.1Hz), 6.84-7.00 (3H, m),
7.70-7.83 (4H, m)

5 21(2)

NMR (CDCl₃) δ : 0.74 (3H, t, J=7.1Hz), 0.98-1.14 (9H, m),
1.42-2.25 (5H, m), 3.63 (2H, s), 3.66 (3H, s), 3.75-4.04
(6H, m), 6.48-6.56 (2H, m), 6.81 (1H, d, J=8.6Hz), 7.35
(1H, d, J=8.8Hz), 7.66-7.76 (2H, m)

10 21(3)

NMR (CDCl₃) δ : 0.76 (6H, d, J=5.9Hz), 0.98 (6H, d, J=6.1Hz),
1.02 (6H, d, J=6.6Hz), 1.17-2.32 (7H, m), 3.63 (2H, s),
3.65 (3H, s), 3.79 (2H, d, J=6.1Hz), 3.88-4.08 (2H, m),
4.04 (2H, t, J=6.6Hz), 6.47-6.56 (2H, m), 6.80
(1H, d, J=8.8Hz), 7.36 (1H, d, J=8.6Hz), 7.64-7.73 (2H, m)

21(4)

NMR (CDCl₃) δ : 0.72 (6H, d, J=6.6Hz), 0.95 (6H, d, J=6.1Hz),
1.05 (6H, d, J=6.6Hz), 1.59-2.05 (5H, m), 3.60-3.81
(6H, m), 3.65 (3H, s), 3.98-4.12 (2H, m), 6.47-6.57
(2H, m), 6.82 (1H, d, J=9.0Hz), 7.36 (1H, d, J=8.3Hz), 7.65-
7.75 (2H, m)

21(5)

NMR (CDCl₃) δ : 0.76 (6H, d, J=5.9Hz), 0.96 (6H, d, J=5.9Hz),
0.99 (6H, d, J=5.9Hz), 1.18-1.73 (9H, m), 3.61 (2H, s),
3.65 (3H, s), 3.81-4.04 (6H, m), 6.47-6.78 (2H, m), 6.83
(1H, d, J=8.5Hz), 7.36 (1H, d, J=8.5Hz), 7.64-7.73 (2H, m)

21(6)

NMR (CDCl₃) δ : 0.74 (6H, d, J=5.6Hz), 0.95-1.34 (15H, m),

1.61-1.73 (3H,m), 2.04-2.30 (4H,m), 2.56-2.64 (2H,m),
2.86-3.05 (2H,m), 3.76-4.24 (8H,m), 6.47-6.56 (2H,m),
6.78 (1H,d,J=9.5Hz), 7.36 (1H,d,J=8.3Hz), 7.58-7.65
(2H,m)

5 21(7)

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.6Hz), 0.93-1.15 (12H,m),
1.23 (3H,t,J=7.1Hz), 1.57-2.35 (5H,m), 2.48-2.67
(2H,m), 2.80-3.02 (2H,m), 3.61 (2H,d,J=6.5Hz), 3.77
(2H,d,J=6.4Hz), 3.99-4.23 (4H,m), 6.46-6.57 (2H,m),

10 6.81 (1H,d,J=8.1Hz), 7.34 (1H,d,J=8.1Hz), 7.59-7.68
(2H,m)

21(8)

NMR (CDCl₃) δ: 1.05 (6H,d,J=6.6Hz), 1.07 (6H,d,J=6.6Hz),
1.23 (3H,t,J=7.1Hz), 1.90-2.30 (2H,m), 2.59-2.71
(2H,m), 2.91-3.12 (2H,m), 3.80 (2H,d,J=6.6Hz), 3.82
(2H,d,J=6.1Hz), 4.13 (2H,q,J=7.1Hz), 6.81-6.99 (3H,m),
7.63-7.82 (4H,m)

15 21(9)

NMR (CDCl₃) δ: 0.74 (6H,d,J=6.1Hz), 0.96 (6H,d,J=6.9Hz),
0.98 (6H,d,J=6.1Hz), 1.23 (3H,t,J=7.1Hz), 1.56-2.04
(9H,m), 2.26-2.67 (2H,m), 2.85-3.02 (2H,m), 3.86-4.23
(8H,m), 6.44-6.56 (2H,m), 6.82 (1H,d,J=8.1Hz), 7.38
(1H,d,J=8.1Hz), 7.58-7.68 (2H,m)

20 21(10)

25 NMR (CDCl₃) δ: 0.72 (6H,d,J=6.6Hz), 1.05
(12H,d,J=6.6Hz), 1.23 (3H,t,J=7.0Hz), 1.90-2.31 (7H,m),
2.68 (2H,t,J=7.3Hz), 3.62 (2H,d,J=6.4Hz), 3.78
(4H,d,J=6.6Hz), 4.11 (2H,q,J=7.2Hz), 6.47-6.59 (2H,m),

6.77 (1H,d,J=9.3Hz), 7.35 (1H,d,J=7.8Hz), 7.58-7.64
(2H,m)

21(11)

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.4Hz), 1.03 (6H,d,J=6.8Hz),

5 1.04 (6H,d,J=6.6Hz), 1.25 (3H,t,J=7.1Hz), 1.68-2.23
(3H,m), 3.50 (2H,d,J=6.8Hz), 3.62 (2H,d,J=6.4Hz), 3.70
(2H,d,J=6.7Hz), 3.79 (2H,d,J=6.4Hz), 4.14
(2H,q,J=7.1Hz), 5.74 (1H,d,J=16.1Hz), 6.47-6.56 (2H,m),
6.80 (1H,d,J=8.3Hz), 6.83-7.18 (1H,m), 7.36

10 (1H,d,J=8.3Hz), 7.60-7.83 (2H,m)

21(12)

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.6Hz), 0.96 (6H,d,J=7.1Hz),

1.05 (6H,d,J=6.8Hz), 1.26 (3H,t,J=7.1Hz), 1.64-2.25
(5H,m), 3.49 (2H,d,J=6.6Hz), 3.62 (2H,d,J=6.4Hz), 3.77
15 (2H,d,J=6.3Hz), 3.98-4.27 (4H,m), 5.75 (1H,d,J=15.3Hz),
6.47-6.56 (2H,m), 6.82 (1H,d,J=7.5Hz), 7.06
(1H,d,J=15.3Hz), 7.39 (1H,d,J=7.2Hz), 7.60-7.72 (2H,m)

21(13)

NMR (CDCl₃) δ: 0.68 (6H,d,J=6.0Hz), 1.05 (6H,d,J=6.6Hz),

20 1.23 (3H,t,J=7.1Hz), 1.50-2.28 (2H,m), 2.34 (3H,s),
2.44-2.94 (4H,m), 3.61 (2H,d,J=6.4Hz), 3.78
(2H,d,J=6.4Hz), 4.12 (2H,q,J=7.1Hz), 6.32-6.57 (2H,m),
7.03-7.67 (4H,m)

Example 22

25 In 18 ml of methylene chloride is dissolved
1.8 g of 2-isobutoxy-4-(isobutoxycarbonyl)-benzoic
acid. After adding 0.7 ml of oxalyl chloride and

subsequently 20 μ l of N,N-dimethylformamide at ambient temperature, the mixture thus obtained is stirred at ambient temperature for one hour. Then, 1.6 g of aluminum chloride and subsequently 1.8 g of ethyl 3-(2-
 5 isobutoxyphenyl)propanoate are added at 5-10°C, and the resulting mixture is stirred at ambient temperature for one hour. The reaction mixture is added to a mixture of chloroform and water and the organic layer is separated. The organic layer thus obtained is washed
 10 with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent;
 15 hexane:ethyl acetate = 5:1) to obtain 2.1 g of isobutyl 4-[3-(3-ethoxy-3-oxopropyl)-4-isobutoxybenzoyl]-3-isobutoxybenzoate as a colorless oily product.

NMR (CDCl_3) δ : 0.74 (6H,d,J=6.6Hz), 1.05 (12H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 1.56-2.36 (3H,m),
 20 2.45-2.66 (2H,m), 2.87-3.06 (2H,m), 3.74 (2H,d,J=6.1Hz), 3.81 (2H,d,J=5.9Hz), 4.11 (2H,q,J=7.1Hz), 4.15 (2H,d,J=6.6Hz), 6.80 (1H,d,J=9.3Hz), 7.36 (1H,d,J=7.8Hz), 7.57-7.76 (4H,m)

Example 23

25 The procedure of Example 22 is repeated to obtain ethyl 3-[5-(2-fluoro-4-isobutoxybenzoyl)-2-isobutoxyphenyl]propanoate.

NMR (CDCl₃) δ : 1.05 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.8Hz),
 1.23 (3H,t,J=7.1Hz), 1.88-2.40 (2H,m), 2.48-2.70
 (2H,m), 2.89-3.11 (2H,m), 3.78 (2H,d,J=6.4Hz), 3.82
 (2H,d,J=6.1Hz), 4.12 (2H,q,J=7.1Hz), 6.57-6.89 (3H,m),
 5 7.50 (1H,t,J=8.5Hz), 7.66-7.98 (2H,m)

Example 24

The procedure of Example 22 is repeated to obtain ethyl 3-{5-[4-(acetyloxy)-2-isobutoxybenzoyl]-2-isobutoxyphenyl}propanoate.

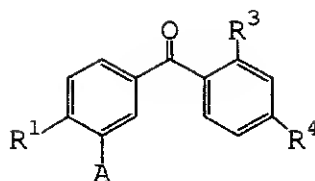
10 NMR (CDCl₃) δ : 0.71 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.8Hz),
 1.23 (3H,t,J=7.1Hz), 1.59-2.35 (2H,m), 2.32 (3H,s),
 2.48-2.67 (2H,m), 2.83-3.07 (2H,m), 3.63
 (2H,d,J=6.4Hz), 3.80 (2H,d,J=6.1Hz), 4.12
 (2H,q,J=6.8Hz), 6.71-6.82 (3H,m), 7.35 (1H,d,J=7.6Hz),
 15 7.58-7.68 (2H,m)

Example 25

The procedure of Example 7 is repeated to obtain the compounds shown in Table 81.

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[Table 81]



No.	R ¹	R ³	R ⁴	A
25 (1)	O-iBu	H	O-iBu	CH ₂ COOH
25 (2)	O-iBu	O-nPr	O-nPr	CH ₂ COOH
25 (3)	O-iBu	O-iAm	O-iAm	CH ₂ COOH
25 (4)	O-iAm	O-iBu	O-iBu	CH ₂ COOH
25 (5)	O-iAm	O-iAm	O-iAm	CH ₂ COOH
25 (6)	O-iBu	O-iAm	O-iAm	(CH ₂) ₂ COOH
25 (7)	O-iAm	O-iBu	O-iBu	(CH ₂) ₂ COOH
25 (8)	O-iBu	H	O-iBu	(CH ₂) ₂ COOH
25 (9)	O-iBu	F	O-iBu	(CH ₂) ₂ COOH
25 (10)	O-iBu	O-iBu	OH	(CH ₂) ₂ COOH
25 (11)	O-iBu	O-iBu	COOH	(CH ₂) ₂ COOH
25 (12)	O-iBu	O-iBu	CONH-iPr	(CH ₂) ₂ COOH
25 (13)	H	O-iBu	O-iBu	(CH ₂) ₂ COOH
25 (14)	O-iAm	O-iAm	O-iAm	(CH ₂) ₂ COOH
25 (15)	O-iBu	O-iBu	O-iBu	(CH ₂) ₃ COOH
25 (16)	O-iBu	O-iBu	O-iBu	CH ₂ CH=CHCOOH
25 (17)	O-iAm	O-iBu	O-iBu	CH ₂ CH=CHCOOH

25(1)

NMR (CDCl₃) δ : 1.04 (12H, d, J=6.6Hz), 1.90-2.35 (2H, m),
3.70 (2H, s), 3.80 (2H, d, J=6.6Hz), 3.82 (2H, d, J=6.3Hz),
6.89-6.99 (3H, m), 7.69-7.82 (5H, m)

5 25(2)

NMR (CDCl₃) δ : 0.71 (3H, t, J=7.1Hz), 0.98-1.14 (9H, m),
1.32-2.18 (5H, m), 3.65 (2H, s), 3.75-4.04 (6H, m), 6.48-
6.57 (2H, m), 6.82 (1H, d, J=8.6Hz), 7.35 (1H, d, J=8.7Hz),
7.64-7.80 (3H, m)

10 25(3)

NMR (CDCl₃) δ : 0.73 (6H, d, J=5.9Hz), 0.98 (6H, d, J=5.9Hz),
1.02 (6H, d, J=6.6Hz), 1.21-2.25 (7H, m), 3.65 (2H, s),
3.79 (2H, d, J=6.1Hz), 3.86 (2H, t, J=6.1Hz), 4.04
(2H, t, J=6.3Hz), 6.47-6.58 (2H, m), 6.82 (1H, d, J=7.8Hz),

15 7.37 (1H, d, J=8.3Hz), 7.64-7.73 (3H, m)

25(4)

NMR (CDCl₃) δ : 0.70 (6H, d, J=6.6Hz), 0.94 (6H, d, J=6.6Hz),
1.04 (6H, d, J=6.6Hz), 1.60-2.25 (5H, m), 3.57-3.80
(4H, m), 3.64 (2H, s), 4.06 (2H, t, J=6.1Hz), 6.46-6.57

20 (2H, m), 6.84 (1H, d, J=8.3Hz), 7.36 (1H, d, J=8.1Hz), 7.63-
7.76 (3H, m)

25(5)

NMR (CDCl₃) δ : 0.73 (6H, d, J=5.9Hz), 0.94 (6H, d, J=5.8Hz),
0.98 (6H, d, J=5.8Hz), 1.26-1.43 (3H, m), 1.64-1.77

25 (6H, m), 3.64 (2H, s), 3.80-4.11 (6H, m), 6.47-6.58

(2H, m), 6.82 (1H, d, J=8.6Hz), 7.36 (1H, d, J=8.3Hz), 7.65-
7.76 (3H, m)

25(6)

NMR (CDCl₃) δ : 0.73 (6H,d,J=5.9Hz), 0.98 (6H,d,J=6.4Hz),
1.06 (6H,d,J=6.8Hz), 1.60-2.30 (7H,m), 2.53-3.08
(4H,m), 3.77-4.24 (6H,m), 6.47-6.59 (2H,m), 6.79
(1H,d,J=9.3Hz), 7.37 (1H,d,J=8.3Hz), 7.60-7.66 (3H,m)

5 25(7)

NMR (CDCl₃) δ : 0.69 (6H,d,J=6.6Hz), 0.93-1.08 (12H,m),
1.59-2.25 (5H,m), 2.58-2.70 (2H,m), 2.85-3.03 (2H,m),
3.61 (2H,d,J=6.4Hz), 3.77 (2H,d,J=6.5Hz), 3.98
(2H,t,J=6.6Hz), 6.46-6.58 (2H,m), 6.80 (1H,d,J=9.1Hz),

10 7.35 (1H,d,J=8.1Hz), 7.60-7.69 (3H,m)

25(8)

NMR (CDCl₃) δ : 1.04 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.6Hz),
1.88-2.39 (2H,m), 2.59-3.12 (4H,m), 3.80
(2H,d,J=6.4Hz), 3.82 (2H,d,J=6.1Hz), 6.82-7.00 (3H,m),

15 7.65-7.81 (4H,m), 9.60 (1H,brs)

25(9)

NMR (CDCl₃) δ : 1.04 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.6Hz),
1.85-2.41 (2H,m), 2.56-3.17 (4H,m), 3.77
(2H,d,J=6.3Hz), 3.82 (2H,d,J=6.3Hz), 6.57-6.90 (3H,m),

20 7.49 (1H,dd,J=8.6,8.3Hz), 7.67-7.76 (2H,m), 8.79

(1H,brs)

25(10)

NMR (CDCl₃) δ : 0.66 (6H,d,J=6.6Hz), 1.04 (6H,d,J=6.6Hz),
1.52-2.28 (2H,m), 2.55-3.04 (4H,m), 3.51

25 (2H,d,J=6.3Hz), 3.79 (2H,d,J=6.1Hz), 6.41-6.47 (2H,m),

6.80 (1H,d,J=8.3Hz), 7.20-7.71 (5H,m)

25(11)

NMR (CDCl₃) δ : 0.74 (6H,d,J=6.6Hz), 1.07 (6H,d,J=6.8Hz),

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5 25(12)

10 7.28-7.66 (5H,m), 9.87 (1H,brs)

NMR (CDCl₃) δ: 0.65 (6H, d, J=6.4Hz), 1.01 (6H, d, J=6.6Hz), 1.55-2.20 (2H, m), 2.35-2.76 (4H, m), 3.78

15 6.83 (1H,d,J=8.1Hz), 7.17-7.45 (3H,m), 10.60 (1H,brs),
11.70 (1H,brs)

NMR (CDCl₃) δ: 0.73 (6H, d, J=6.9Hz), 0.98 (12H, d, J=6.1Hz), 1.26-1.47 (3H, m), 1.66-1.95 (6H, m), 2.59-2.70 (2H, m), 2.86-3.04 (2H, m), 3.79-4.11 (6H, m), 6.47-6.59 (2H, m), 6.81 (1H, d, J=9.2Hz), 7.36 (1H, d, J=8.3Hz), 7.59-7.67 (3H, m)

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.6Hz), 1.05 (12H,
d,J=6.6Hz), 1.68-2.18 (5H,m), 2.41 (2H,t,J=7.1Hz), 2.70
(2H,t,J=7.6Hz), 3.62 (2H,d,J=6.4Hz), 3.77
(4H,d,J=6.4Hz), 6.47-6.58 (2H,m), 6.78 (1H,d,J=9.3Hz),
7.36 (1H,d,J=7.8Hz), 7.59-7.65 (3H,m)

25 (16)

NMR (CDCl₃) δ : 0.71 (6H, d, J=6.8Hz), 1.05
 (12H, d, J=6.6Hz), 1.63-2.30 (3H, m), 3.30 (2H, d, J=7.7Hz),
 3.63 (2H, d, J=7.3Hz), 3.75 (2H, d, J=2.8Hz), 3.83
 5 (2H, d, J=2.7Hz), 6.42-6.56 (3H, m), 6.72-6.90 (3H, m),
 7.36 (1H, d, J=8.5Hz), 7.65 (1H, dd, J=8.7, 2.4Hz), 7.89
 (1H, d, J=2.0Hz)

25 (17)

NMR (CDCl₃) δ : 0.71 (6H, d, J=6.6Hz), 0.98 (6H, d, J=6.4Hz),
 10 1.05 (6H, d, J=6.7Hz), 1.69-2.25 (5H, m), 3.29
 (2H, d, J=6.8Hz), 3.63 (2H, d, J=6.3Hz), 3.78
 (2H, d, J=6.3Hz), 4.07 (2H, t, J=6.3Hz), 6.40-6.55 (3H, m),
 6.70-6.89 (2H, m), 7.38 (1H, d, J=7.2Hz), 7.65
 (1H, dd, J=10.8, 2.2Hz), 7.89 (1H, d, J=2.0Hz), 8.23
 15 (1H, brs)

Example 26

In 2 ml of methylene chloride is dissolved
 0.15 g of 4-[3-(2-carboxyethyl)-4-isobutoxybenzoyl]-3-
 isobutoxybenzoic acid, to which is added 0.12 g of
 20 1,1'-carbonyldiimidazole. After stirring the mixture
 at ambient temperature for one hour, 15 μ l of methanol
 is added, and the mixture thus obtained is stirred at
 the same temperature as above for one hour. Ethyl
 acetate and water are added to the reaction mixture, pH
 25 is adjusted to 2 with 2 mol/L hydrochloric acid, and
 the organic layer is separated. The organic layer is
 washed with water and saturated aqueous solution of

sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure to obtain 0.05 g of 3-isobutoxy-4-[4-isobutoxy-3-(3-methoxy-3-oxopropyl)benzoyl]benzoic acid as a white solid product.

NMR (CDCl_3) δ : 0.75 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.6Hz), 1.70-2.28 (2H,m), 2.48-3.05 (4H,m), 3.66 (3H,s), 3.76 (2H,d,J=6.4Hz), 3.81 (2H,d,J=6.4Hz), 6.82 (1H,d,J=9.3Hz), 7.31 (1H,d,J=8.6Hz), 7.45-7.84 (5H,m)

10 Example 27

In 2.5 ml of methylene chloride is dissolved 0.25 g of 3-isobutoxy-4-[4-isobutoxy-3-(3-methoxy-3-oxopropyl)benzoyl]benzoic acid. At ambient temperature, 60 μl of oxalyl chloride is added and then 20 μl of N,N-dimethylformamide is added, and the mixture thus obtained is stirred at ambient temperature for one hour. The reaction mixture is cooled with ice water, 0.12 ml of isopropylamine is dropwise added thereto, and the mixture thus obtained is stirred at ambient temperature for one hour. Ethyl acetate and water are added to the reaction mixture, pH is adjusted to 2 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure to obtain 0.12 g of methyl 3-(2-isobutoxy-5-

{2-isobutoxy-4-[(isopropylamino)carbonyl]benzoyl}-phenyl)propanoate as a white solid product.

NMR (CDCl₃) δ : 0.69 (6H,d,J=6.4Hz), 1.05 (6H,d,J=6.6Hz), 1.29 (6H,d,J=6.6Hz), 1.64-2.35 (2H,m), 2.50-2.66
 5 (2H,m), 2.87-3.04 (2H,m), 3.65 (3H,s), 3.73-3.83 (4H,m), 4.07-4.50 (1H,m), 6.54 (1H,brs), 6.80 (1H,d,J=9.3Hz), 7.30-7.62 (5H,m)

Example 28

To a solution of 17 g of 2-(2-
 10 isobutoxyphenyl)ethanal in 170 ml of acetonitrile, 29 g of sodium dihydrogenphosphate dissolved in 200 ml of water and subsequently 15 g of 30% aqueous hydrogen peroxide are added, and further 16 g of sodium chlorite dissolved in 80 ml of water is dropwise added, and the
 15 mixture thus obtained is stirred at ambient temperature for one hour. Ethyl acetate and water added to the reaction mixture, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and
 20 dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is mixed with 22 g of potassium carbonate and 200 ml of N,N-dimethylformamide. While cooling the mixture with ice water, 19 g of iodomethane is added,
 25 and the mixture thus obtained is stirred at ambient temperature for 30 minutes. Ethyl acetate and water are added to the reaction mixture, and the organic

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layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced
 5 pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to obtain 10.4 g of methyl 2-(2-isobutoxyphenyl)acetate as a colorless oily product.
 NMR (CDCl₃) δ : 1.02 (6H,d,J=6.8Hz), 1.85-2.30 (1H,m),
 10 3.64-3.76 (4H,m), 3.67 (3H,s), 6.79-7.02 (1H,m), 6.83 (1H,d,J=7.6Hz), 7.15-7.25 (1H,m), 7.19 (1H,d,J=7.1Hz)

Example 29

The procedure of Example 16 is repeated to obtain 3-[5-(2,4-diisobutoxybenzyl)-2-isobutoxyphenyl]-
 15 propanoic acid.

NMR (CDCl₃) δ : 0.96-0.98 (18H,m), 1.82-2.25 (3H,m),
 2.50-2.65 (2H,m), 2.71-3.00 (2H,m), 3.65-3.72 (6H,m),
 3.82 (2H,s), 6.30-6.42 (2H,m), 6.69 (1H,d,J=9.0Hz),
 6.88-7.02 (3H,m), 9.88 (1H,brs)

20 Example 30

The procedure of Example 16 is repeated to obtain 3-[5-(2-hydroxy-4-isobutoxybenzyl)-2-isobutoxyphenyl]propanoic acid.

NMR (CDCl₃) δ : 0.95-1.06 (12H,m), 1.89-2.24 (2H,m),
 25 2.53-2.71 (2H,m), 2.83-3.04 (2H,m), 3.69 (2H,d,J=6.6Hz), 3.69 (2H,d,J=6.3Hz), 3.82 (2H,s), 6.36-

7.02 (7H,m), 6.71 (1H,d,J=9.0Hz)

Example 31

The procedure of Example 16 is repeated to obtain 2-[5-(3,4-diisopentyloxybenzyl)-2-

5 isopentyloxyphenyl]acetic acid.

NMR (CDCl₃) δ: 0.91-0.97 (18H,m), 1.62-1.92 (9H,m), 3.61 (2H,s), 3.83-4.04 (8H,m), 6.60-7.10 (7H,m)

Example 32

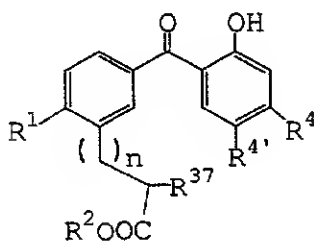
In 15 ml of methylene chloride is dissolved
10 1.50 g of methyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]acetate, to which is added 1.06 g of aluminum chloride at ambient temperature. The mixture is stirred at ambient temperature for 2 hours. The reaction mixture is added to a mixture of chloroform
15 and ice water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced
20 pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 0.62 g of methyl 2-[5-(2-hydroxy-4-isobutoxybenzoyl)-2-isobutoxyphenyl]acetate as a yellow-colored solid product.
25 NMR (CDCl₃) δ: 1.04 (12H,d,J=6.6Hz), 1.90-2.33 (2H,m), 3.70-3.86 (9H,m), 6.38-6.49 (2H,m), 6.91 (1H,d,J=8.8Hz),

7.53-7.67 (3H,m), 12.64 (1H,s)

Example 33

The procedure of Example 32 is repeated to obtain the compounds shown in Table 82.

[Table 82]



No.	n	R ¹	R ⁴	R ^{4'}	R ²	R ³⁷
33(1)	0	O-iBu	O-iAm	H	Me	H
33(2)	0	O-iBu	O-nPr	H	Me	H
33(3)	0	O-iAm	O-iAm	H	Me	H
33(4)	1	O-iBu	O-iBu	H	Me	H
33(5)	1	O-iAm	O-iAm	H	Et	H
33(6)	1	O-iAm	O-iBu	H	Et	H
33(7)	1	O-iBu	O-iBu	H	Et	Me
33(8)	1	O-iBu	H	O-iBu	Et	H

5 33(1)

NMR (CDCl₃) δ: 0.97 (6H,d,J=5.9Hz), 1.04 (6H,d,J=6.8Hz),
1.59-2.34 (4H,m), 3.70 (5H,s), 3.82 (2H,d,J=6.4Hz),
4.05 (2H,t,J=6.3Hz), 6.37-6.51 (2H,m), 6.91
(1H,d,J=8.3Hz), 7.52-7.65 (3H,m), 12.66 (1H,s)

33(2)

NMR (CDCl₃) δ : 0.96-1.12 (9H,m), 1.56-2.04 (3H,m), 3.70 (3H,s), 3.79-4.06 (6H,m), 6.35-6.51 (2H,m), 6.90 (1H,d,J=9.0Hz), 7.52-7.67 (3H,m), 12.65 (1H,s).

5 33(3)

NMR (CDCl₃) δ : 0.97 (12H,d,J=6.1Hz), 1.57-1.77 (6H,m), 3.67 (2H,s), 3.70 (3H,s), 4.05 (2H,t,J=6.6Hz), 4.08 (2H,t,J=6.6Hz), 6.35-6.51 (2H,m), 6.94 (1H,d,J=8.5Hz), 7.52-7.65 (3H,m), 12.66 (1H,s)

10 33(4)

NMR (CDCl₃) δ : 1.03 (6H,d,J=6.6Hz), 1.07 (6H,d,J=6.6Hz), 1.90-2.40 (2H,m), 2.58-3.32 (4H,m), 3.67 (3H,s), 3.78 (2H,d,J=6.6Hz), 3.82 (2H,d,J=6.1Hz), 6.35-6.48 (2H,m), 6.88 (1H,d,J=9.0Hz), 7.51-7.59 (3H,m), 12.69 (1H,s)

15 33(5)

NMR (CDCl₃) δ : 0.94-1.02 (12H,m), 1.23 (3H,t,J=7.1Hz), 1.65-1.76 (6H,m), 2.53-2.69 (2H,m), 2.90-3.08 (2H,m), 4.01-4.28 (6H,m), 6.34-6.51 (2H,m), 6.90 (1H,d,J=9.3Hz), 7.50-7.59 (3H,m), 12.70 (1H,s)

20 33(6)

NMR (CDCl₃) δ : 1.00 (6H,d,J=5.9Hz), 1.04 (6H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 1.72-2.34 (4H,m), 2.51-3.12 (4H,m), 3.79 (2H,d,J=6.6Hz), 4.02-4.25 (4H,m), 6.38-6.51 (2H,m), 6.91 (1H,d,J=8.2Hz), 7.52-7.60 (3H,m),

25 12.69 (1H,s)

33(7)

NMR (CDCl₃) δ : 1.00-1.26 (18H,m), 1.98-2.33 (2H,m), 2.63-3.17 (3H,m), 3.79 (2H,d,J=6.4Hz), 3.88

(2H,d,J=6.3Hz), 4.09 (2H,q,J=7.1Hz), 6.34-6.48 (2H,m),
6.89 (1H,d,J=8.3Hz), 7.49-7.59 (3H,m), 12.69 (1H,s)

33(8)

NMR (CDCl₃) δ: 0.95-1.12 (12H,m), 1.22 (3H,t,J=7.1Hz),

5 1.83-2.32 (2H,m), 2.52-3.08 (4H,m), 3.62

(2H,d,J=6.4Hz), 3.85 (2H,d,J=6.4Hz), 4.13

(2H,q,J=6.8Hz), 6.85-7.27 (4H,m), 7.59-7.66 (2H,m),

11.46 (1H,s)

Example 34

10 In 3 ml of N,N-dimethylformamide are
suspended 0.28 g of methyl 2-[5-(2-hydroxy-4-
isobutoxybenzoyl)-2-isobutoxyphenyl]acetate, 0.32 g of
potassium carbonate and 0.23 ml of isopentyl iodide.
The suspension is stirred at 120°C for 2 hours. The
15 reaction mixture is added to a mixture of ethyl acetate
and water, pH is adjusted to 2 with 6 mol/L
hydrochloric acid, and the organic layer is separated.
The organic layer thus obtained is washed with water
and saturated aqueous solution of sodium chloride
20 successively and dried over anhydrous magnesium
sulfate, and the solvent is distilled off under reduced
pressure. The residue thus obtained is purified by
silica gel column chromatography (eluent; hexane:ethyl
acetate = 5:1) to obtain 0.17 g of methyl 2-[5-(4-
25 isobutoxy-2-isopentyloxybenzoyl)-2-isobutoxyphenyl]-
acetate as a colorless oily product.

NMR (CDCl₃) δ: 0.75 (6H,d,J=5.6Hz), 1.02 (6H,d,J=6.6Hz),

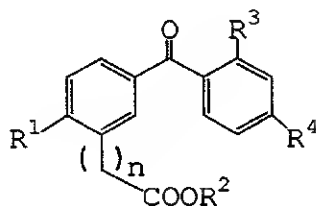
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1.05 (6H,d,J=6.8Hz), 1.26-1.55 (3H,m), 1.90-2.25
 (2H,m), 3.62-3.94 (11H,m), 6.47-6.55 (2H,m), 6.80
 (1H,d,J=8.3Hz), 7.36 (1H,d,J=8.5Hz), 7.63-7.72 (2H,m)

Example 35

- 5 The procedure of Example 34 is repeated to
 obtain the compounds shown in Table 83.

[Table 83]



No.	n	R ¹	R ³	R ⁴	R ²
35(1)	1	O-iBu	O-iBu	O-iAm	Me
35(2)	1	O-iBu	O-nPr	O-iBu	Me
35(3)	1	O-iBu	O-iBu	O-nPr	Me
35(4)	1	O-iAm	O-iBu	O-iAm	Me
35(5)	2	O-iBu	O-Me	O-iBu	Me
35(6)	2	O-iBu	O-(CH ₂) ₃ CO ₂ Et	O-iBu	Me
35(7)	2	O-iBu	O-(CH ₂) ₅ CONH ₂	O-iBu	Me
35(8)	2	O-iBu	O-C(O)-iPr	O-iBu	H

NMR (CDCl₃) δ: 0.73 (6H, d, J=6.6Hz), 0.99 (6H, d, J=6.1Hz), 1.02 (6H, d, J=6.8Hz), 1.51-2.31 (5H, m), 3.59-3.63 (4H, m), 3.65 (3H, s), 3.79 (2H, d, J=6.4Hz), 4.04

35 (2)

10 (2H,m), 3.62-3.90 (8H,m), 3.65 (3H,s), 6.47-6.58
(2H,m), 6.82 (1H,d,J=8.3Hz), 7.34 (1H,d,J=8.8Hz), 7.65-
7.77 (2H,m)

NMR (CDCl₃) δ: 0.73 (6H, d, J=6.8Hz), 0.98-1.14 (9H, m),

15 1.65-2.25 (4H,m), 3.59-3.82 (6H,m), 3.65 (3H,s), 3.97 (2H,t,J=6.6Hz), 6.47-6.58 (2H,m), 6.80 (1H,d,J=8.3Hz), 7.35 (1H,d,J=7.8Hz), 7.65-7.77 (2H,m)

35 (4)

NMR (CDCl₃) δ: 0.72 (6H, d, J=6.6Hz), 0.91 (6H, d, J=5.9Hz),

20 0.95 (6H,d,J=5.9Hz), 1.57-1.93 (7H,m), 3.59-3.65
(4H,m), 3.65 (3H,s), 4.04 (4H,t,J=6.3Hz), 6.46-6.57
(2H,m), 6.83 (1H,d,J=8.0Hz), 7.36 (1H,d,J=8.0Hz), 7.65-
7.75 (2H,m)

35 (5)

25 NMR (CDCl₃) δ : 1.06 (12H,d,J=6.6Hz), 1.91-2.36 (2H,m),
2.51-2.69 (2H,m), 2.88-3.08 (2H,m), 3.67 (3H,s), 3.73
(3H,s), 3.77-3.84 (4H,m), 6.48-6.56 (2H,m), 6.81
(1H,d,J=9.0Hz), 7.31 (1H,dd,J=8.5,1.0Hz), 7.63-7.71

(2H,m)

35(6)

NMR (CDCl₃) δ : 1.05 (12H,d,J=6.6Hz), 1.22

(3H,t,J=7.1Hz), 1.72-2.30 (6H,m), 2.50-2.67 (2H,m),

5 2.87-3.07 (2H,m), 3.67 (3H,s), 3.74-4.20 (9H,m), 6.48-
6.60 (2H,m), 6.80 (1H,d,J=9.3Hz), 7.36 (1H,d,J=9.4Hz),
7.59-7.65 (2H,m)

35(7)

NMR (CDCl₃) δ : 0.89-1.09 (14H,m), 1.40-1.80 (4H,m),

10 2.00-2.26 (4H,m), 2.51-2.69 (2H,m), 2.88-3.06 (2H,m),
3.66 (3H,s), 3.74-3.95 (6H,m), 5.48 (1H,brs), 5.90
(1H,brs), 6.47-6.55 (2H,m), 6.80 (1H,d,J=9.3Hz), 7.32
(1H,d,J=8.3Hz), 7.60-7.66 (2H,m)

35(8)

15 NMR (CDCl₃) δ : 1.03 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.6Hz),
1.13 (6H,d,J=5.9Hz), 1.62-3.10 (7H,m), 3.77
(2H,d,J=6.3Hz), 3.80 (2H,d,J=6.4Hz), 6.66
(1H,d,J=2.2Hz), 6.80 (1H,d,J=8.6Hz), 6.82
(1H,d,J=9.5Hz), 7.43 (1H,d,J=8.6Hz), 7.52-7.71 (2H,m),
20 7.90 (1H,brs)

Example 36

In 2 ml of methanol is dissolved 0.13 g of
methyl 2-[5-(4-isobutoxy-2-isopentyloxybenzoyl)-2-
isobutoxyphenyl]acetate, to which is added 0.2 ml of 5
25 mol/L solution of sodium hydroxide. The mixture thus
obtained is stirred at ambient temperature for one hour
and then at 50-60°C for one hour. Chloroform and water

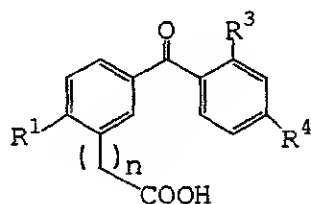
are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to obtain 0.07 g of 2-[5-(4-isobutoxy-2-isopentyloxybenzoyl)-2-isobutoxyphenyl]acetic acid as a white-colored solid product.

NMR (CDCl_3) δ : 0.73 (6H,d,J=5.9Hz), 1.01 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.6Hz), 1.20-1.50 (3H,m), 1.90-2.33 (2H,m), 3.64-3.93 (8H,m), 6.47-6.57 (2H,m), 6.81 (1H,d,J=8.3Hz), 7.36 (1H,d,J=8.8Hz), 7.64-7.75 (2H,m), 9.18 (1H,brs)

Example 37

The procedure of Example 36 is repeated to obtain the compounds shown in Table 84.

[Table 84]



No.	n	R ¹	R ³	R ⁴
37 (1)	1	O-iBu	O-iBu	O-iAm
37 (2)	1	O-iBu	O-nPr	O-iBu
37 (3)	1	O-iBu	O-iBu	O-nPr
37 (4)	1	O-iAm	O-iBu	O-iAm
37 (5)	2	O-iBu	O-Me	O-iBu
37 (6)	2	O-iBu	O-(CH ₂) ₃ CO ₂ H	O-iBu
37 (7)	2	O-iBu	O-(CH ₂) ₅ CONH ₂	O-iBu

37 (1)

NMR (CDCl₃) δ: 0.70 (6H, d, J=6.6Hz), 0.98 (6H, d, J=5.9Hz),
 1.01 (6H, d, J=6.6Hz), 1.65-2.32 (5H, m), 3.58-3.64
 (4H, m), 3.79 (2H, d, J=6.3Hz), 4.04 (2H, t, J=6.6Hz), 6.46-
 5 6.55 (3H, m), 6.82 (1H, d, J=8.3Hz), 7.36 (1H, d, J=8.1Hz),
 7.65-7.77 (2H, m)

37 (2)

NMR (CDCl₃) δ: 0.71 (3H, t, J=7.3Hz), 1.02 (6H, d, J=6.6Hz),
 1.05 (6H, d, J=6.6Hz), 1.42-1.62 (2H, m), 1.97-2.25
 10 (2H, m), 3.65 (2H, s), 3.73-3.89 (6H, m), 6.47-6.58
 (2H, m), 6.83 (1H, d, J=8.3Hz), 7.35 (1H, d, J=8.8Hz), 7.63-
 7.79 (3H, m)

37 (3)

NMR (CDCl₃) δ : 0.70 (6H,d,J=6.6Hz), 0.97-1.14 (9H,m),
1.63-2.25 (4H,m), 3.58-3.82 (6H,m), 3.97
(2H,t,J=6.6Hz), 6.46-6.58 (2H,m), 6.82 (1H,d,J=8.3Hz),
7.35 (1H,d,J=8.5Hz), 7.63-7.77 (3H,m)

5 37(4)

NMR (CDCl₃) δ : 0.82 (6H,d,J=6.8Hz), 0.93 (6H,d,J=5.9Hz),
0.98 (6H,d,J=5.9Hz), 1.54-1.94 (7H,m), 3.57-3.64
(4H,m), 4.04 (2H,t,J=6.1Hz), 4.06 (2H,t,J=6.1Hz), 6.44-
6.58 (2H,m), 6.85 (1H,d,J=8.3Hz), 7.37 (1H,d,J=8.2Hz),

10 7.66-7.78 (3H,m)

37(5)

NMR (CDCl₃) δ : 1.05 (12H,d,J=6.6Hz), 1.84-2.34 (2H,m),
2.55-3.09 (4H,m), 3.72 (3H,s), 3.74-3.84 (4H,m), 6.46-
6.58 (2H,m), 6.81 (1H,d,J=9.3Hz), 7.30 (1H,d,J=9.0Hz),

15 7.64-7.74 (2H,m), 8.06 (1H,brs)

37(6)

NMR (CDCl₃) δ : 1.01 (12H,d,J=6.6Hz), 1.55-2.20 (6H,m),
2.37-2.54 (2H,m), 2.75-2.92 (2H,m), 3.80-3.97 (6H,m),
6.57-6.66 (2H,m), 6.98 (1H,d,J=9.0Hz), 7.25

20 (1H,d,J=8.8Hz), 7.44-7.51 (2H,m), 11.98 (2H,brs)

37(7)

NMR (CDCl₃) δ : 0.98-1.05 (12H,m), 1.20-1.50 (6H,m),
1.80-2.20 (4H,m), 2.40-2.60 (2H,m), 2.75-2.90 (2H,m),
3.40 (2H,brs), 3.81-3.88 (6H,m), 6.57-6.64 (2H,m),

25 6.94-7.31 (3H,m), 7.48-7.50 (2H,m)

Example 38

In 155 ml of ethanol is dissolved 30.9 g of

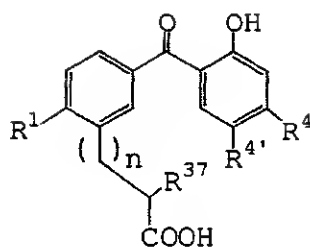
methy1 3-[5-(2-hydroxy-4-isobutoxybenzoyl)-2-isobutoxyphenyl]propanoate, to which is added 44 ml of 5 mol/L solution of sodium hydroxide. The mixture is stirred at ambient temperature for one hour. Water, followed by chloroform, is added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 29.5 g of 3-[5-(2-hydroxy-4-isobutoxybenzoyl)-2-isobutoxyphenyl]-propanoic acid is obtained as a yellow-white colored solid product.

NMR (CDCl₃) δ: 1.02 (6H,d,J=6.6Hz), 1.07 (6H,d,J=6.6Hz), 1.89-2.39 (2H,m), 2.63-2.79 (2H,m), 2.93-3.10 (2H,m), 3.77 (2H,d,J=6.4Hz), 3.82 (2H,d,J=6.1Hz), 6.39-6.48 (2H,m), 6.89 (1H,d,J=9.0Hz), 7.48-7.62 (3H,m), 9.76 (1H,brs), 12.67 (1H,s)

Example 39

The procedure of Example 38 is repeated to obtain the compounds shown in Table 85.

[Table 85]



No.	n	R ¹	R ⁴	R ^{4'}	R ³⁷
39(1)	1	O-iAm	O-iAm	H	H
39(2)	1	O-iAm	O-iBu	H	H
39(3)	1	O-iBu	O-iBu	H	Me
39(4)	1	O-iBu	H	O-iBu	H
39(5)	0	O-iBu	O-iBu	H	H
39(6)	0	O-iBu	O-iAm	H	H

39(1)

NMR (CDCl₃) δ: 0.95 (12H, d, J=6.6Hz), 1.52-2.00 (6H, m),
2.64-2.94 (4H, m), 3.89-4.09 (4H, m), 6.33-6.45 (2H, m),
6.80-6.90 (1H, m), 7.46-7.54 (4H, m), 12.50 (1H, brs)

5 39(2)

NMR (CDCl₃) δ: 0.99 (6H, d, J=5.6Hz), 1.02 (6H, d, J=6.6Hz),
1.56-2.26 (4H, m), 2.51-3.13 (4H, m), 3.78
(2H, d, J=6.6Hz), 4.08 (2H, t, J=5.9Hz), 6.36-6.48 (2H, m),
6.90 (1H, d, J=9.0Hz), 7.49-7.58 (3H, m), 9.25 (1H, brs),

10 12.67 (1H, s)

39(3)

NMR (CDCl₃) δ: 0.98-1.23 (15H, m), 1.88-2.27 (2H, m),
2.63-3.16 (3H, m), 3.73-3.80 (4H, m), 6.32-6.39 (2H, m),

6.88 (1H,d,J=8.5Hz), 7.46-7.60 (3H,m), 9.00 (1H,brs),
12.66 (1H,brs)

39(4)

NMR (CDCl₃) δ: 0.95-1.12 (12H,m), 1.82-2.40 (2H,m),
5 2.61-3.27 (4H,m), 3.63 (2H,d,J=6.3Hz), 3.85
(2H,d,J=6.4Hz), 6.86-7.27 (4H,m), 7.61-7.67 (2H,m),
9.38 (1H,brs), 11.45 (1H,brs)

39(5)

NMR (CDCl₃) δ: 1.01 (12H,d,J=6.8Hz), 1.90-2.30 (2H,m),
10 3.70-3.84 (6H,m), 6.33-6.46 (2H,m), 6.90
(1H,d,J=8.3Hz), 7.49-7.64 (3H,m), 10.22 (1H,brs), 12.60
(1H,brs)

39(6)

NMR (CDCl₃) δ: 0.94-1.07 (12H,m), 1.62-2.27 (4H,m), 3.72
15 (2H,s), 3.83 (2H,d,J=6.4Hz), 4.05 (2H,t,J=6.2Hz), 6.33-
6.51 (2H,m), 6.92 (1H,d,J=8.1Hz), 7.51-7.66 (4H,m),
12.64 (1H,s)

Example 40

In 11 ml of methylene chloride is dissolved
20 1.11 g of 3,5-diisobutoxybenzoic acid. To the solution
thus obtained, 0.44 ml of oxalyl chloride is added at
ambient temperature, and then 20 µl of N,N-
dimethylformamide is added and stirred at ambient
temperature for 2 hours. Then, at -20°C, 1.67 g of
25 aluminum chloride is added and thereafter 1.15 g of
ethyl 3-(2-isobutoxyphenyl)propanoate is added, and the
mixture thus obtained is stirred at 5-10°C for 10

minutes. The reaction mixture is added to a mixture of chloroform and ice water, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride

5 successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 1.75 g of ethyl 3-[5-(3,5-

10 diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoate as a yellow-colored oily product.

NMR (CDCl₃) δ: 0.98-1.26 (18H,m), 1.23 (3H,t,J=7.1Hz), 1.86-2.33 (3H,m), 2.51-2.74 (2H,m), 2.93-3.14 (2H,m), 3.70-3.86 (6H,m), 4.12 (2H,q,J=7.1Hz), 6.63-6.91

15 (4H,m), 7.65-7.84 (2H,m)

Example 41

In 9 ml of ethanol is dissolved 1.74 g of ethyl 3-[5-(3,5-diisobutoxybenzoyl)-2-isobutoxyphenyl]-propanoate. After adding 2 ml of 5 mol/L solution of

20 sodium hydroxide, the mixture thus obtained is stirred at ambient temperature for one hour. Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is successively

25 washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced

pressure. Thus, 1.53 g of 3-[5-(3,5-diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoic acid is obtained as a white solid product.

NMR (CDCl₃) δ: 0.98-1.11 (18H,m), 1.86-2.38 (3H,m),
5 2.58-3.18 (4H,m), 3.70-3.87 (6H,m), 6.60-6.91 (4H,m),
7.68-7.88 (2H,m), 8.58 (1H,brs)

Example 42

In 50 ml of methylene chloride is dissolved 5.00 g of 2,5-diisobutoxybenzoic acid. After adding
10 2.0 ml of oxalyl chloride and subsequently 20 µl of N,N-dimethylformamide at ambient temperature, the mixture thus obtained is stirred at ambient temperature for one hour. Then, 7.51 g of aluminum chloride and subsequently 5.17 g of ethyl 3-(2-isobutoxyphenyl)-
15 propanoate are added at -30°C, the mixture thus obtained is stirred at -10°C for 10 minutes. The reaction mixture is added to a mixture of chloroform and ice water and the organic layer is separated. The organic layer thus obtained is washed with water and saturated
20 aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to
25 obtain 9.21 g of ethyl 3-[5-(2,5-diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoate as a yellow-colored oily product.

NMR (CDCl₃) δ : 0.70 (6H,d,J=6.6Hz), 1.00 (6H,d,J=6.6Hz),
 1.05 (6H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 1.62-2.35
 (3H,m), 2.46-2.66 (2H,m), 2.87-3.06 (2H,m), 3.59
 (2H,d,J=6.4Hz), 3.69 (2H,d,J=6.4Hz), 3.80
 5 (2H,d,J=6.4Hz), 4.12 (2H,q,J=7.1Hz), 6.74-7.06 (4H,m),
 7.56-7.75 (2H,m)

Example 43

In 26 ml of ethanol is dissolved 5.2 g of
 ethyl 3-[5-(2,5-diisobutoxybenzoyl)-2-isobutoxyphenyl]-
 10 propanoate. After adding 6 ml of 5 mol/L aqueous
 solution of sodium hydroxide, the mixture is stirred at
 ambient temperature for 30 minutes. Chloroform and
 water are added to the reaction mixture, pH is adjusted
 to 2 with 6 mol/L hydrochloric acid, and the organic
 15 layer is separated. The organic layer is washed with
 water and saturated aqueous solution of sodium chloride
 successively, and the solvent is distilled off from the
 reaction mixture under reduced pressure. Thus, 4.9 g
 of 3-[5-(2,5-diisobutoxybenzoyl)-2-isobutoxyphenyl]-
 20 propanoic acid is obtained as a yellow solid product.
 NMR (CDCl₃) δ : 0.69 (6H,d,J=6.6Hz), 1.00 (6H,d,J=6.6Hz),
 1.05 (6H,d,J=6.4Hz), 1.60-2.29 (3H,m), 2.50-3.13
 (4H,m), 3.58 (2H,d,J=6.4Hz), 3.69 (2H,d,J=6.6Hz), 3.80
 (2H,d,J=6.4Hz), 6.76-6.91 (4H,m), 7.61-7.69 (2H,m),
 25 8.28 (1H,brs)

Example 44

In 8 ml of methylene chloride is dissolved 0.80 g of 3,4-diisopentyloxybenzoic acid. Then, 20 μ l of N,N-dimethylformamide is added, and the mixture thus obtained is stirred at ambient temperature for one hour. To the mixture thus obtained are successively added 1.10 g of aluminum chloride and 0.95 g of isopentyl 2-(2-isopentyloxyphenyl)acetate at 5-10°C, and the mixture thus obtained is stirred at 5-10°C for 10 minutes. The reaction mixture is added to a mixture of chloroform and ice water, and the organic layer is separated. After washing the organic layer with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography [eluent; hexane:ethyl acetate = 10:1] to obtain 1.20 g of isopentyl 2-[5-(3,4-diisopentyloxybenzoyl)-2-isopentyloxyphenyl]-acetate as a yellow oily product.

NMR (CDCl_3) δ : 0.86-1.00 (24H,m), 1.46-1.95 (12H,m), 3.64 (2H,s), 4.00-4.19 (8H,m), 6.84-6.93 (2H,m), 7.26-7.41 (2H,m), 7.69-7.78 (2H,m)

Example 45

The procedure of Example 44 is repeated to obtain ethyl 3-[5-(3,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoate.

NMR (CDCl₃) δ : 1.01-1.14 (18H,m), 1.23 (3H,t,J=7.1Hz),
 1.90-2.36 (3H,m), 2.47-2.81 (2H,m), 2.86-3.14 (2H,m),
 3.77-3.86 (6H,m), 4.12 (2H,q,J=7.1Hz), 6.81-6.91
 (2H,m), 7.26-7.38 (2H,m), 7.64-7.71 (2H,m)

5 Example 46

In 12 ml of ethanol is dissolved 1.20 g of
 isopentyl 2-[5-(3,4-diisopentyloxybenzoyl)-2-
 isopentyloxyphenyl]acetate. After adding 0.6 ml of 5
 mol/L aqueous solution of sodium hydroxide, the mixture
 10 is stirred at 50°C for one hour. Chloroform and water
 are added to the reaction mixture, pH is adjusted to 2
 with 6 mol/L hydrochloric acid, and the organic layer
 is separated. The organic layer is washed with water
 and saturated aqueous solution of sodium chloride
 15 successively, and the solvent is distilled off from the
 reaction mixture under reduced pressure. Thus, 0.88 g
 of 2-[5-(3,4-diisopentyloxybenzoyl)-2-
 isopentyloxyphenyl]acetic acid is obtained as a white
 solid product.

20 NMR (CDCl₃) δ : 0.96 (12H,d,J=5.6Hz), 0.98
 (6H,d,J=5.9Hz), 1.59-1.78 (9H,m), 3.70 (2H,s), 4.00-
 4.16 (6H,m), 6.88 (1H,d,J=8.3Hz), 6.92 (1H,d,J=8.8Hz),
 7.26-7.43 (2H,m), 7.71-7.82 (2H,m), 9.35 (1H,brs)

Example 47

25 The procedure of Example 46 is repeated to
 obtain 3-[5-(3,4-diisobutoxybenzoyl)-2-

isobutoxyphenyl]-propanoic acid.

NMR (CDCl₃) δ : 1.06 (18H,d,J=6.6Hz), 1.92-2.50 (3H,m),
2.65-3.24 (4H,m), 3.82 (6H,d,J=6.6Hz), 6.82-6.92
(2H,m), 7.26-7.40 (2H,m), 7.65-7.73 (2H,m), 8.54
5 (1H,brs)

Example 48

In 10 ml of methylene chloride is dissolved
.1.00 g of 3-(acetyloxy)-4-isobutoxybenzoic acid. After
adding 0.41 ml of oxalyl chloride and 20 μ l of N,N-
10 dimethylformamide successively at ambient temperature,
the mixture thus obtained is stirred at ambient
temperature for one hour. Then, 1.06 g of aluminum
chloride and 1.15 g of 1,3-diisobutoxybenzene are
successively added at 5-10°C, and the mixture is stirred
15 at the same temperature as above for one hour. The
reaction mixture is added to a mixture of methylene
chloride and ice water, and the organic layer is
separated. The organic layer is successively washed
with water and saturated aqueous solution of sodium
20 chloride and dried over anhydrous magnesium sulfate,
and the solvent is distilled off under reduced
pressure. The residue thus obtained is purified by
silica gel column chromatography [eluent; n-
hexane:ethyl acetate = 5:1] to obtain 1.24 g of 5-(2,4-
25 diisobutoxybenzoyl)-2-isobutoxyphenyl acetate as a
yellow oily product.

NMR (CDCl₃) δ : 0.73 (6H,d,J=6.8Hz), 1.00 (6H,d,J=6.8Hz),

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- 1.05 (6H,d,J=6.6Hz), 1.65-2.40 (3H,m), 2.28 (3H,s),
 3.63 (2H,d,J=6.3Hz), 3.77 (2H,d,J=6.4Hz), 3.80
 (2H,d,J=6.4Hz), 6.46-6.57 (2H,m), 6.91 (1H,d,J=8.5Hz),
 7.35 (1H,d,J=8.6Hz), 7.47 (1H,d,J=2.2Hz), 7.67
 5 (1H,dd,J=8.6,2.2Hz)

Example 49

The procedure of Example 48 is repeated to obtain ethyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isopentyloxyphenoxy]acetate.

- 10 NMR (CDCl₃) δ : 0.72 (6H,d,J=6.6Hz), 0.97 (6H,d,J=6.4Hz),
 1.05 (6H,d,J=6.8Hz), 1.28 (3H,t,J=7.1Hz), 1.70-2.34
 (5H,m), 3.62 (2H,d,J=6.4Hz), 3.77 (2H,d,J=6.4Hz), 4.10
 (2H,t,J=6.6Hz), 4.24 (2H,q,J=7.1Hz), 4.66 (2H,s), 6.46-
 6.55 (2H,m), 6.85 (1H,d,J=9.0Hz), 7.29-7.42 (3H,m)

15 Example 50

The procedure of Example 48 is repeated to obtain ethyl 2-[5-(2,4-diisopentyloxybenzoyl)-2-isopentyloxyphenoxy]acetate.

- NMR (CDCl₃) δ : 0.77 (6H,d,J=5.6Hz), 0.98
 20 (12H,d,J=5.9Hz), 1.28 (3H,t,J=7.1Hz), 1.64-2.04 (9H,m),
 3.88-4.36 (8H,m), 4.66 (2H,s), 6.47-6.55 (2H,m), 6.85
 (1H,d,J=9.0Hz), 7.29-7.38 (3H,m)

Example 51

- In 10 ml of ethanol is dissolved 0.48 g of 5-
 25 (2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl acetate, to

which is added 3.2 ml of 1 mol/L solution of sodium hydroxide. The mixture thus obtained is stirred at ambient temperature for one hour. Water and chloroform are added to the reaction mixture, pH is adjusted to 2
5 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried on anhydrous magnesium sulfate, and the solvent is distilled off under reduced
10 pressure. Thus, 0.40 g of (2,4-diisobutoxyphenyl)(3-hydroxy-4-isobutoxyphenyl)methanone is obtained as a light yellow solid product.

NMR (CDCl₃) δ: 0.72 (6H,d,J=6.8Hz), 1.04
(12H,d,J=6.6Hz), 1.60-2.30 (3H,m), 3.63 (2H,d,J=6.4Hz),
15 3.76 (2H,d,J=6.6Hz), 3.86 (2H,d,J=6.6Hz), 5.59 (1H,s),
6.46-6.56 (2H,m), 6.81 (1H,d,J=8.8Hz), 7.26-7.39 (3H,m)

Example 52

In 9 ml of N,N-dimethylformamide is dissolved 0.86 g of (2,4-diisobutoxyphenyl)(3-hydroxy-4-
20 isobutoxyphenyl)methanone, to which is added 0.12 g of 60% sodium hydride. After elevating the temperature to 80°C, 0.52 ml of ethyl 2-bromoacetate is added, and the mixture thus obtained is stirred at 80-90°C for 30 minutes. The reaction mixture is cooled to ambient
25 temperature and added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic

layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 1.00 g of ethyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenoxy]acetate as a light yellow oily product.

10 NMR (CDCl_3) δ : 0.72 (6H,d,J=6.6Hz), 1.05 (12H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 1.50-2.33 (3H,m), 3.62 (2H,d,J=6.1Hz), 3.76 (2H,d,J=5.6Hz), 3.83 (2H,d,J=6.4Hz), 4.24 (2H,q,J=7.1Hz), 4.66 (2H,s), 6.46-6.58 (2H,m), 6.84 (1H,d,J=9.0Hz), 7.27-7.43 (3H,m)

15 Example 53

In 10 ml of ethanol is dissolved 0.95 g of ethyl 2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenoxy]acetate, to which is added 5.7 ml of 1 mol/L solution of sodium hydroxide. The mixture thus obtained is stirred at ambient temperature for one hour. Water and chloroform are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous

25 solution of sodium chloride successively and dried on anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 0.83 g of

2-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenoxy]acetic acid is obtained as a white solid product.

NMR (CDCl₃) δ: 0.71 (6H,d,J=6.6Hz), 1.05 (12H,d,J=6.6Hz), 1.55-2.40 (3H,m), 3.62 (2H,d,J=6.1Hz), 3.78 (2H,d,J=6.6Hz), 3.85 (2H,d,J=6.8Hz), 4.68 (2H,s), 6.45-6.58 (2H,m), 6.88 (1H,d,J=9.0Hz), 7.32-7.52 (3H,m), 8.50 (1H,brs)

Example 54

The procedure of Example 53 is repeated to obtain 2-[5-(2,4-diisobutoxybenzoyl)-2-isopentyloxyphenoxy]acetic acid.

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.6Hz), 0.98 (6H,d,J=6.1Hz), 1.05 (6H,d,J=6.6Hz), 1.52-2.34 (5H,m), 3.62 (2H,d,J=6.4Hz), 3.77 (2H,d,J=6.6Hz), 4.12 (2H,t,J=6.6Hz), 4.67 (2H,s), 6.45-6.59 (3H,m), 6.89 (1H,d,J=9.0Hz), 7.33-7.53 (3H,m)

Example 55

The procedure of Example 53 is repeated to obtain 2-[5-(2,4-diisopentyloxybenzoyl)-2-isopentyloxyphenoxy]acetic acid.

NMR (CDCl₃) δ: 0.75 (6H,d,J=6.1Hz), 0.98 (12H,d,J=6.1Hz), 1.18-1.52 (3H,m), 1.60-2.04 (6H,m), 3.87 (2H,t,J=6.1Hz), 4.04 (2H,t,J=6.6Hz), 4.12 (2H,t,J=6.8Hz), 4.66 (2H,s), 5.65 (1H,brs), 6.45-6.59 (2H,m), 6.89 (1H,d,J=9.0Hz), 7.33-7.49 (3H,m)

Example 56

In 40 ml of tetrahydrofuran is dissolved 4.00 g of 5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoic acid, to which are added 0.95 ml of oxalyl chloride and 5 20 μ l of N,N-dimethylformamide. The mixture thus obtained is stirred at ambient temperature for one hour. To the reaction mixture are added 3.03 g of glycine ethyl ester hydrochloride and 4.2 ml of triethylamine successively, and the mixture thus 10 obtained is stirred for one hour under reflux with heating. The reaction mixture is cooled to ambient temperature, chloroform and water are added, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous 15 solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to 20 obtain 4.00 g of ethyl 2-([5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoyl]amino)acetate as a colorless oily product.

NMR (CDCl_3) δ : 0.66 (6H,d,J=6.6Hz), 1.04 (6H,d,J=6.1Hz), 1.10 (6H,d,J=5.1Hz), 1.29 (3H,t,J=7.1Hz), 1.92-2.55 25 (3H,m), 3.62 (2H,d,J=6.1Hz), 3.76 (2H,d,J=6.6Hz), 3.99 (2H,d,J=6.4Hz), 4.12-4.36 (4H,m), 6.46-6.56 (2H,m), 7.01 (1H,d,J=8.8Hz), 6.97-7.15 (1H,m), 7.92-8.07 (1H,m), 8.29-8.51 (2H,m)

Example 57

In 7 ml of ethanol is dissolved 0.64 g of ethyl 2-([5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoyl]amino)acetate, to which is added 0.73 ml of 5 mol/L solution of sodium hydroxide. The mixture thus obtained is stirred at ambient temperature for one hour. Water and ethyl acetate are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated.

The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; chloroform:ethanol = 20:1) to obtain 0.25 g of 2-([5-(2,4-diisobutoxybenzoyl)-2-isobutoxybenzoyl]amino)-acetic acid as a white solid product.

NMR (DMSO- d_6) δ : 0.61 (6H,d,J=6.6Hz), 1.01 (12H,d,J=6.4Hz), 1.42-2.40 (3H,m), 3.68 (2H,d,J=6.1Hz), 3.84 (2H,d,J=6.4Hz), 4.00-4.06 (4H,m), 6.59-6.66 (2H,m), 7.22-7.35 (2H,m), 7.80 (1H,d,J=7.8Hz), 8.17 (1H,d,J=2.0Hz), 8.34-8.48 (1H,m), 12.76 (1H,brs)

Example 58

In 10 ml of tetrahydrofuran is dissolved 1.00 g of 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-propanoic acid, to which is added 0.52 g of 1,1'-

5 sulfonamide and 0.4 ml of 1,8-diazabicyclo[5.4.0]undec-
7-ene, and the mixture thus obtained is stirred for 30
minutes at ambient temperature. The reaction mixture
is added to a mixture of chloroform and water, pH is
adjusted to 2 with 6 mol/L hydrochloric acid, and the
10 organic layer is separated. The organic layer thus
obtained is washed with water and saturated aqueous
solution of sodium chloride successively and dried over
anhydrous magnesium sulfate, and the solvent is
distilled off under reduced pressure. The residue thus
15 obtained is purified by silica gel column
chromatography (eluent; hexane:ethyl acetate = 2:1) to
obtain 1.10 g of N-{3-[5-(2,4-diisobutoxybenzoyl)-2-
isobutoxyphenyl]propanoyl}methanesulfonamide as a
white-colored foaming product.

20 NMR (CDCl₃) δ: 0.68 (6H,d,J=6.6Hz), 1.03 (12H,d,J=6.6Hz), 1.54-2.35 (3H,m), 2.46-3.20 (4H,m), 3.23 (3H,s), 3.60 (2H,d,J=6.4Hz), 3.73-3.80 (4H,m), 6.45-6.55 (2H,m), 6.78 (1H,d,J=8.5Hz), 7.31 (1H,d,J=8.3Hz), 7.53-7.64 (2H,m), 8.94 (1H,brs)

In 100 ml of tetrahydrofuran is dissolved
10.6 g of ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-

isobutoxyphenyl]propanoate, to which is dropwise added at -60°C a solution of lithium diisopropylamide in 30 ml tetrahydrofuran (prepared from 88 ml of 1.6 mol/L solution of n-butyllithium in n-hexane and 17 ml of isopropylamine). The mixture thus obtained is stirred at the same temperature as above for one hour. After dropping the reaction mixture thus obtained at -60°C into a solution of 26 ml of methyl iodide in 30 ml of tetrahydrofuran, the temperature is elevated to ambient temperature over a period of one hour. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 4.9 g of ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-2-methylpropanoate as a colorless oily product.

NMR (CDCl₃) δ: 0.71 (6H,d,J=6.8Hz), 1.02-1.30 (18H,m), 1.57-2.30 (3H,m), 2.46-3.15 (3H,m), 3.62 (2H,d,J=6.4Hz), 3.78 (4H,d,J=6.1Hz), 3.97-4.25 (2H,m), 6.46-6.60 (3H,m), 7.34 (1H,d,J=8.3Hz), 7.58-7.70 (2H,m)

Example 60

In 3 ml of ethanol is dissolved 0.55 g of

ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-
 2-methylpropanoate, to which is added 1.5 ml of 5 mol/L
 solution of sodium hydroxide. The mixture thus
 obtained is stirred at ambient temperature for two
 5 hours. Chloroform and water are added to the reaction
 mixture, pH is adjusted to 2 with 6 mol/L hydrochloric
 acid, and the organic layer is separated. The organic
 layer thus obtained is washed with water and saturated
 aqueous solution of sodium chloride successively and
 10 dried over anhydrous magnesium sulfate, and the solvent
 is distilled off under reduced pressure. The residue
 thus obtained is purified by silica gel column
 chromatography (eluent; n-hexane:ethyl acetate = 2:1)
 to obtain 0.45 g of 3-[5-(2,4-diisobutoxybenzoyl)-2-
 15 isobutoxyphenyl]-2-methylpropanoic acid as a white
 solid product.

NMR (CDCl₃) δ: 0.70 (6H,d,J=6.6Hz), 0.88-1.26 (15H,m),
 1.61-2.33 (3H,m), 2.54-3.25 (3H,m), 3.61
 (2H,d,J=6.3Hz), 3.77 (4H,d,J=6.4Hz), 6.46-6.58 (2H,m),
 20 6.79 (1H,d,J=9.0Hz), 7.24 (1H,brs), 7.35
 (1H,d,J=8.1Hz), 7.60-7.71 (2H,m)

Example 61

In 20 ml of ethanol is dissolved 10.00 g of
 ethyl 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]-
 25 propanoate, to which are added 5.59 g of hydroxylamine
 hydrochloride and 7 ml of pyridine. The mixture is
 heated under reflux for 4.5 hours with stirring. After

cooling the mixture to ambient temperature, chloroform and water are added, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 5:1) to obtain 10.20 g of ethyl 3-{5-[(2,4-diisobutoxyphenyl)(hydroxyimino)-methyl]-2-isobutoxyphenyl}propanoate as a light brown oily product.

NMR (CDCl₃) δ: 0.72-1.30 (21H,m), 1.62-2.33 (3H,m), 2.42-3.00 (4H,m), 3.46-3.79 (6H,m), 4.10 (2H,q,J=7.3Hz), 6.39-6.82 (3H,m), 7.04-7.31 (3H,m), 7.99 (1H,brs)

Example 62

The procedure of Example 61 is repeated to obtain isopentyl 2-{5-[(3,4-diisopentyloxyphenyl)-(hydroxyimino)methyl]-2-isopentyloxyphenyl}acetate.

NMR (CDCl₃) δ: 0.86-0.98 (24H,m), 1.46-1.92 (12H,m), 3.56-3.61 (2H,m), 3.93-4.17 (8H,m), 6.75-6.95 (3H,m), 7.17-7.40 (3H,m), 8.20 (1H,brs)

Example 63

The procedure of Example 61 is repeated to obtain 2-{5-[(3,4-diisopentyloxyphenyl)-

(hydroxyimino)methyl]-2-isopentyloxyphenyl}acetic acid.

NMR (CDCl₃) δ: 0.91-0.97 (18H,m), 1.57-1.93 (9H,m),
3.68-3.71 (2H,m), 3.88-4.13 (6H,m), 5.20 (1H,brs),
6.73-7.60 (7H,m)

5 Example 64

The procedure of Example 61 is repeated to
obtain methyl 3-{5-[(2-hydroxy-4-isobutoxyphenyl)-
(hydroxyimino)methyl]-2-isobutoxyphenyl}propanoate.

Further, isomers are separated by silica gel column
10 chromatography (eluent; hexane:ethyl acetate = 5:1).

Less polar oxime:

NMR (CDCl₃) δ: 1.00 (6H,d,J=6.4Hz), 1.07 (6H,d,J=6.4Hz),
1.92-2.31 (2H,m), 2.56-2.73 (2H,m), 2.92-3.09 (2H,m),
3.65 (3H,s), 3.70 (2H,d,J=6.6Hz), 3.80 (2H,d,J=6.1Hz),
15 6.30 (1H,dd,J=8.8,2.4Hz), 6.51 (1H,d,J=2.4Hz), 6.75
(1H,d,J=8.8Hz), 6.90 (1H,d,J=8.8Hz), 7.11-7.26 (2H,m),
7.44 (1H,s), 11.33 (1H,s)

More polar oxime:

NMR (CDCl₃) δ: 1.03 (6H,d,J=6.8Hz), 1.05 (6H,d,J=6.6Hz),
20 1.94-2.26 (2H,m), 2.44-2.62 (2H,m), 2.80-2.96 (2H,m),
3.64 (3H,s), 3.76 (4H,d,J=6.4Hz), 6.45
(1H,dd,J=8.8,2.4Hz), 6.59 (1H,d,J=2.2Hz), 6.75
(1H,d,J=9.0Hz), 6.85 (1H,d,J=9.0Hz), 7.18-7.26 (2H,m),
7.49 (2H,brs)

Example 65

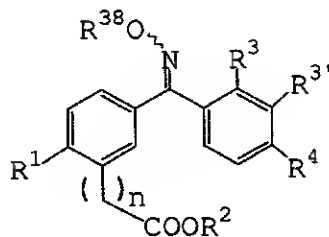
In 5 ml of N,N-dimethylformamide is dissolved 2.0 g of ethyl 3-{5-[(2,4-diisobutoxyphenyl)-(hydroxyimino)methyl]-2-isobutoxyphenyl}propanoate, to which is added 0.19 g of 60% sodium hydride. The mixture thus obtained is stirred at ambient temperature for 30 minutes. Then, 1.07 g of 2-bromoacetamide is added and the mixture thus obtained is stirred at ambient temperature for one hour and further at 80°C for 15 minutes. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to obtain 1.09 g of ethyl 3-{5-[(2-amino-2-oxoethoxy)imino](2,4-diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoate as a colorless oily product.

NMR (CDCl₃) δ: 0.79 (6H,d,J=6.8Hz), 1.05 (12H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 1.60-2.40 (3H,m), 2.44-2.67 (2H,m), 2.80-3.05 (2H,m), 3.47-3.80 (6H,m), 4.11 (2H,q,J=7.3Hz), 4.61 (2H,s), 5.45-5.61 (1H,m), 6.42-7.02 (5H,m), 7.19-7.39 (2H,m)

Example 66

The procedure of Example 65 is repeated to obtain the compounds shown in Table 86.

[Table 86]



No.	n	R ¹	R ³	R ^{3'}	R ⁴	R ³⁸	R ²
66(1)	1	O-iAm	H	O-iAm	O-iAm	CH ₂ CO ₂ Et	iAm
66(2)	1	O-iAm	H	O-iAm	O-iAm	CH ₂ CONH ₂	iAm
66(3)	2	O-iBu	OH	H	O-iBu	CH ₂ Ph	Me
66(4)	2	O-iBu	OH	H	O-iBu	CH ₂ -3-Py	Me
66(5)	2	O-iBu	OH	H	O-iBu	CH ₂ CONH ₂	Me
66(6)	1	O-iAm	H	O-iAm	O-iAm	nPr	iAm

66(1)

- 5 NMR (CDCl₃) δ: 0.86-0.98 (24H,m), 1.29 (3H,t,J=7.1Hz),
1.42-1.93 (12H,m), 3.56-3.59 (2H,m), 3.86-4.36 (10H,m),
4.70 (2H,s), 6.70-7.53 (6H,m)

66(2)

- 10 NMR (CDCl₃) δ: 0.87-0.99 (24H,m), 1.42-1.93 (12H,m),
3.57-3.62 (2H,m), 3.97-4.18 (8H,m), 4.63-4.64 (2H,m),
5.56 (1H,brs), 6.15 (1H,brs), 6.71-6.94 (3H,m), 7.20-
7.40 (3H,m)

66(3)

NMR (CDCl₃) δ : 0.99 (6H,d,J=6.6Hz), 1.06 (6H,d,J=7.6Hz),
 1.90-2.31 (2H,m), 2.54-2.71 (2H,m), 2.90-3.06 (2H,m),
 3.64 (3H,s), 3.68 (2H,d,J=7.3Hz), 3.79 (2H,d,J=6.3Hz),
 5 5.10 (2H,s), 6.26 (1H,dd,J=8.8,2.4Hz), 6.47
 (1H,d,J=2.5Hz), 6.70 (1H,d,J=8.8Hz), 6.87
 (1H,d,J=8.8Hz), 7.06-7.34 (7H,m), 11.11 (1H,s)

66(4)

NMR (CDCl₃) δ : 0.99 (6H,d,J=7.1Hz), 1.07 (6H,d,J=6.8Hz),
 10 1.92-2.31 (2H,m), 2.71 (2H,t,J=6.8Hz), 2.98
 (2H,t,J=6.8Hz), 3.64 (3H,s), 3.68 (2H,d,J=8.4Hz), 3.79
 (2H,d,J=6.1Hz), 5.14 (2H,s), 6.28 (1H,dd,J=4.7,2.4Hz),
 6.47 (1H,d,J=2.4Hz), 6.70 (1H,d,J=8.8Hz), 6.88
 (1H,d,J=8.5Hz), 7.04-7.36 (3H,m), 7.62-7.72 (1H,m),
 15 8.50-8.54 (2H,m), 10.97 (1H,s)

66(5)

NMR (CDCl₃) δ : 1.00 (6H,d,J=6.6Hz), 1.08 (6H,d,J=6.8Hz),
 1.95-2.33 (2H,m), 2.60-2.74 (2H,m), 2.91-3.07 (2H,m),
 3.62 (3H,s), 3.72 (2H,d,J=6.6Hz), 3.81 (2H,d,J=6.4Hz),
 20 4.58 (2H,s), 5.64 (1H,brs), 6.05 (1H,brs), 6.31
 (1H,dd,J=8.7,2.4Hz), 6.52 (1H,d,J=2.4Hz), 6.72
 (1H,d,J=8.8Hz), 6.91 (1H,d,J=8.8Hz), 7.08-7.21 (2H,m),
 10.63 (1H,s)

Example 67

25 In 10 ml of ethanol is dissolved 1.08 g of
 ethyl 3-{5-[[(2-amino-2-oxoethoxy)imino] (2,4-
 diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoate,

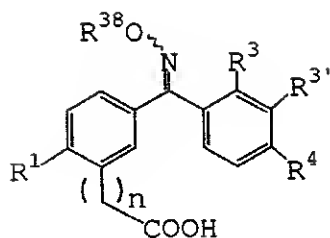
to which is added 1.1 ml of 5 mol/L sodium hydroxide solution. The mixture is stirred at ambient temperature for 3 hours. Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6
5 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off
10 under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; chloroform:ethanol = 10:1) to obtain 0.68 g of 3-{5-
[[(2-amino-2-oxoethoxy) imino] (2,4-
diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoic
15 acid as a white foaming product.
NMR (CDCl₃) δ: 0.63-1.09 (18H,m), 1.51-2.35 (3H,m),
2.47-3.09 (4H,m), 3.47-3.79 (6H,m), 4.59-4.65 (2H,m),
6.40-7.65 (9H,m)

Example 68

20 The procedure of Example 67 is repeated to obtain the compounds shown in Table 87.

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[Table 87]



No.	n	R ¹	R ³	R ^{3'}	R ⁴	R ³⁸
68 (1)	1	O-iAm	H	O-iAm	O-iAm	nPr
68 (2)	1	O-iAm	H	O-iAm	O-iAm	CH ₂ CO ₂ H
68 (3)	1	O-iAm	H	O-iAm	O-iAm	CH ₂ CONH ₂
68 (4)	2	O-iBu	OH	H	O-iBu	CH ₂ Ph
68 (5)	2	O-iBu	OH	H	O-iBu	CH ₂ -3-Py
68 (6)	2	O-iBu	OH	H	O-iBu	CH ₂ CO ₂ H
68 (7)	2	O-iBu	OH	H	O-iBu	CH ₂ CONH ₂
68 (8)	2	O-iBu	OH	H	O-iBu	H
68 (9)	2	O-iBu	O-iBu	H	O-iBu	H

68 (1)

NMR (CDCl₃) δ: 0.92-0.98 (21H,m), 1.68-1.94 (11H,m),
3.63 (2H,s), 3.93-4.20 (8H,m), 6.78-7.48 (7H,m)

68 (2)

- 5 NMR (CDCl₃) δ: 0.90-0.96 (18H,m), 1.57-1.92 (9H,m), 3.64
(2H,s), 3.89-4.18 (6H,m), 4.73 (2H,s), 6.75-7.41
(6H,m), 8.77 (2H,brs)

68 (3)

- 10 NMR (CDCl₃) δ: 0.92-0.99 (18H,m), 1.61-1.72 (9H,m), 3.67
(2H,s), 3.90-4.12 (6H,m), 4.61-4.68 (2H,m), 6.20
(1H,brs), 6.59 (1H, brs), 6.74-7.60 (7H,m)

68(4)

NMR (CDCl₃) δ : 0.96 (6H,d,J=6.8Hz), 1.06 (6H,d,J=6.8Hz),
 1.80-2.30 (2H,m), 2.60-2.75 (2H,m), 2.90-3.05 (2H,m),
 3.67 (2H,d,J=6.4Hz), 3.78 (2H,d,J=6.4Hz), 5.09 (2H,s),
 5 6.27 (1H,dd,J=9.0,2.4Hz), 6.47 (1H,d,J=2.5Hz), 6.71
 (1H,d,J=8.8Hz), 6.87 (1H,d,J=9.0Hz), 7.07-7.33 (8H,m),
 11.00 (1H,brs)

68(5)

NMR (CDCl₃) δ : 0.98 (6H,d,J=6.6Hz), 1.07 (6H,d,J=7.1Hz),
 10 1.83-2.40 (2H,m), 2.71 (2H,t,J=6.6Hz), 3.03
 (2H,t,J=6.6Hz), 3.68 (2H,d,J=6.6Hz), 3.80
 (2H,d,J=6.4Hz), 5.16 (2H,s), 6.26 (1H,dd,J=8.8,2.4Hz),
 6.46 (1H,d,J=2.4Hz), 6.71 (1H,d,J=8.8Hz), 6.89
 (1H,d,J=9.3Hz), 7.07-7.40 (4H,m), 7.60-7.73 (1H,m),
 15 8.40-8.48 (3H,m)

68(6)

NMR (CDCl₃) δ : 0.99 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.1Hz),
 1.92-2.37 (2H,m), 2.64-2.78 (2H,m), 2.92-3.09 (2H,m),
 3.70 (2H,d,J=6.6Hz), 3.78 (2H,d,J=7.1Hz), 4.65 (2H,s),
 20 6.30 (1H,dd,J=8.8,2.4Hz), 6.50 (1H,d,J=2.2Hz), 6.78
 (1H,d,J=8.8Hz), 6.87 (1H,d,J=8.8Hz), 7.10
 (1H,dd,J=8.8,2.0Hz), 7.38 (1H,d,J=1.5Hz), 10.30
 (3H,brs)

68(7)

NMR (CDCl₃) δ : 1.00 (6H,d,J=6.8Hz), 1.07 (6H,d,J=6.8Hz),
 1.93-2.29 (2H,m), 2.67-3.00 (4H,m), 3.67-3.83 (4H,m),
 4.54 (2H,s), 6.23-6.36 (3H,m), 6.50 (1H,d,J=2.2Hz),
 6.73 (1H,d,J=8.8Hz), 6.88 (1H,d,J=9.0Hz), 6.99-7.25

(3H,m), 10.60 (1H,brs)

68(8)

Isomers were separated by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1), and NMR spectra were measured.

Less polar oxime

NMR (DMSO-d₆) δ : 0.96 (6H,d,J=6.8Hz), 1.03

(6H,d,J=6.6Hz), 1.78-2.21 (2H,m), 2.49-2.85 (4H,m),

3.69-3.86 (4H,m), 6.29-6.46 (2H,m), 6.71

(1H,d,J=8.6Hz), 6.94-7.08 (4H,m), 11.70 (2H,brs)

More polar oxime

NMR (DMSO-d₆) δ : 1.00 (12H,d,J=6.6Hz), 1.80-2.17 (2H,m),

2.47-2.80 (4H,m), 3.74 (4H,d,J=3.9Hz), 6.41-6.47

(2H,m), 6.80-7.15 (3H,m), 7.39-7.40 (1H,m), 9.20

(1H,brs), 11.50 (2H,brs)

68(9)

NMR (CDCl₃) δ : 0.73 (6H,d,J=6.6Hz), 1.00-1.07 (12H,m),

1.78-2.31 (3H,m), 2.69-3.00 (4H,m), 3.59-3.76 (6H,m),

6.40-6.80 (3H,m), 7.05-7.28 (2H,m), 7.49 (1H,s), 8.76

(2H,brs)

Example 69

At 5°C, 5.56 g of nickel (II) chloride hexahydrate is added to a solution of 6.00 g of ethyl 3-{5-[(2,4-diisobutoxyphenyl)(hydroxyimino)methyl]-2-isobutoxyphenyl}propanoate in 60 ml of methanol. Then, 4.42 g of sodium borohydride is portionwise added over a period of one hour. Water is added to the reaction

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1 mixture, and then 6 mol/L hydrochloric acid is dropwise
added and stirred at ambient temperature for 10
minutes. pH is adjusted to 9 with saturated aqueous
solution of sodium bicarbonate, methylene chloride is
5 added, and the organic layer is separated. The organic
layer thus obtained is washed with water and saturated
aqueous solution of sodium chloride successively and
dried over anhydrous magnesium sulfate, and the solvent
is distilled off under reduced pressure. Thus, 4.97 g
10 of ethyl 3-{5-[amino(2,4-diisobutoxyphenyl)methyl]-2-
isobutoxyphenyl}propanoate is obtained as a brown oily
product.

NMR (CDCl₃) δ: 0.94-1.06(18H,m), 1.22 (3H,t,J=7.1Hz),
1.66-2.29 (5H,m), 2.44-2.69 (2H,m), 2.79-3.05 (2H,m),
15 3.68 (6H,d,J=6.4Hz), 4.09 (2H,q,J=7.1Hz), 5.36 (1H,s),
6.32-6.50 (2H,m), 6.73 (1H,d,J=9.0Hz), 7.02-7.28 (3H,m)

Example 70

To a solution of 1.10 g of ethyl 3-{5-
[amino(2,4-diisobutoxyphenyl)methyl]-2-
20 isobutoxyphenyl}propanoate in 11 ml of methylene
chloride are dropwise added 0.4 ml of triethylamine and
0.2 ml of methanesulfonyl chloride successively at 5-
10°C. The mixture thus obtained is stirred at the same
temperature as above for 3 hours. Methylene chloride
25 and water are added to the reaction mixture, and the
organic layer is separated. The organic layer thus
obtained is washed with water and saturated aqueous

solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 1.26 g of ethyl 3-(5-{2,4-diisobutoxyphenyl}[(methylsulfonyl)-amino]methyl)-2-isobutoxyphenyl)propanoate is obtained as a yellow-brown colored oily product.

NMR (CDCl₃) δ : 0.78-1.30 (21H,m), 1.72-2.31 (3H,m), 2.40-3.15 (4H,m), 2.65 (3H,s), 3.63-3.80 (6H,m), 4.09 (2H,q,J=7.1Hz), 5.40 (1H,d,J=8.3Hz), 5.69 (1H,d,J=8.3Hz), 6.39-6.57 (2H,m), 6.71 (1H,d,J=8.3Hz), 7.02-7.31 (3H,m)

Example 71

The procedure of Example 70 is repeated to obtain ethyl 3-{5-[(acetylamino)(2,4-diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoate.

NMR (CDCl₃) δ : 0.84-1.06 (18H,m), 1.22 (3H,t,J=7.1Hz), 1.71-2.22 (3H,m), 2.03 (3H,s), 2.22-2.71 (2H,m), 2.78-3.08 (2H,m), 3.61-3.74 (6H,m), 4.09 (2H,q,J=7.1Hz), 6.18-6.72 (5H,m), 6.93-7.15 (3H,m)

Example 72

The procedure of Example 70 is repeated to obtain ethyl 3-{5-[[aminocarbonyl]amino](2,4-diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoate.

NMR (CDCl₃) δ : 0.85-1.06 (18H,m), 1.21 (3H,t,J=7.1Hz), 1.83-2.29 (3H,m), 2.40-2.60 (2H,m), 2.79-3.08 (2H,m), 3.61-3.72 (6H,m), 4.08 (2H,q,J=7.1Hz), 4.47 (2H,brs),

5.41 (1H,d,J=6.8Hz), 5.93 (1H,d,J=6.8Hz), 6.37-6.45
(2H,m), 6.60-6.73 (1H,m), 7.00-7.15 (3H,m)

Example 73

In 7 ml of ethanol is dissolved 1.26 g of
5 ethyl 3-(5-((2,4-diisobutoxyphenyl)[(methylsulfonyl)-
amino]methyl)-2-isobutoxyphenyl)propanoate, to which is
added 1.3 ml of 5 mol/L solution of sodium hydroxide.
The mixture is stirred at ambient temperature for one
hour. Water and chloroform are added to the reaction
10 mixture, pH is adjusted to 2 with 6 mol/L hydrochloric
acid, and the organic layer is separated. The organic
layer is washed with water and saturated aqueous
solution of sodium chloride successively and dried over
anhydrous magnesium sulfate, and the solvent is
15 distilled off under reduced pressure. The residue thus
obtained is purified by silica gel column
chromatography (eluent; hexane:ethyl acetate = 1:1) to
obtain 0.92 g of 3-(5-((2,4-
diisobutoxyphenyl)[(methylsulfonyl)amino]methyl)-2-
20 isobutoxyphenyl)propanoic acid as a light yellow oily
product.

NMR (CDCl₃) δ: 0.80-1.06 (18H,m), 1.80-2.30 (3H,m),
2.44-3.07 (4H,m), 2.66 (3H,s), 3.58-3.81 (6H,m), 5.73
(2H,brs), 6.39-6.58 (2H,m), 6.71 (1H,d,J=9.3Hz), 7.02-
25 7.25 (3H,m), 8.78 (1H,brs)

Example 74

The procedure of Example 73 is repeated to obtain 3-{5-[(acetylamino)(2,4-diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoic acid.

NMR (CDCl₃) δ : 0.83-1.04 (18H,m), 1.89-2.25 (6H,m), 2.55-3.00 (4H,m), 3.57-3.80 (6H,m), 6.20-7.19 (8H,m), 9.04 (1H,brs)

Example 75

The procedure of Example 73 is repeated to obtain 3-{5-[[[(aminocarbonyl)amino](2,4-diisobutoxyphenyl)methyl]-2-isobutoxyphenyl}propanoic acid.

NMR (CDCl₃) δ : 0.87-1.04 (18H,m), 1.84-2.28 (3H,m), 2.48-3.07 (4H,m), 3.04-3.70 (6H,m), 5.20 (2H,brs), 5.90-6.03 (2H,m), 6.39-7.18 (7H,m)

Example 76

In 5 ml of N,N-dimethylformamide is suspended 0.85 g of 60% sodium hydride, to which is dropwise added 4.2 ml of ethyl diethylphosphonoacetate at ambient temperature over a period of 10 minutes. After stirring the mixture thus obtained for 30 minutes, 1.00 g of 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoic acid is added and stirred at 110°C for 5 hours. The reaction mixture is cooled to ambient temperature and added to a mixture of ethyl

acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium

5 sulfate, and the solvent is distilled off under reduced pressure. The residue is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 4:1) to obtain 0.36 g of 3-{5-[1-(2,4-diisobutoxyphenyl)-3-ethoxy-3-oxo-1-propenyl]-2-isobutoxyphenyl}propanoic
10 acid as a light yellow oily product.

NMR (CDCl₃) δ: 0.70-1.30 (21H,m), 1.56-2.33 (3H,m), 2.47-3.05 (4H,m), 3.52-3.76 (6H,m), 3.91-4.21 (2H,m), 6.17-7.18 (7H,m), 8.44 (1H,brs)

Example 77

15 The procedure of Example 76 is repeated to obtain 2-{5-[1-(3,4-diisopentyloxyphenyl)-3-ethoxy-3-oxo-1-propenyl]-2-isobutoxyphenyl}acetic acid.

NMR (CDCl₃) δ: 0.92-0.98 (18H,m), 1.13 (3H,t,J=7.1Hz), 1.56-1.94 (9H,m), 3.64 (2H,s), 3.89-4.09 (8H,m), 6.21
20 (1H,s), 6.78-7.08 (7H,m)

Example 78

In a mixture of 7 ml of ethanol and 3 ml of tetrahydrofuran is dissolved 0.79 g of 3-{5-[1-(2,4-diisobutoxyphenyl)-3-ethoxy-3-oxo-1-propenyl]-2-isobutoxyphenyl}propanoic acid. After adding 8 ml of 5
25 mol/L sodium hydroxide solution, the mixture thus

obtained is stirred at ambient temperature for 2.5 hours and then at 60°C for 1.5 hours. Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 2:1) to obtain 0.58 g of 3-[3-(2-carboxyethyl)-4-isobutoxyphenyl]-3-(2,4-diisobutoxyphenyl)-2-propenoic acid as a light yellow foaming product.

NMR (CDCl₃) δ: 0.70-1.06 (18H,m), 1.60-2.33 (3H,m), 2.40-3.07 (4H,m), 3.56 (2H,d,J=6.1Hz), 3.72 (4H,d,J=6.1Hz), 6.16-7.12 (7H,m), 9.36 (2H,brs)

Example 79

In 6 ml of ethanol is dissolved 0.60 g of 3-{5-[1-(2,4-diisobutoxyphenyl)-3-ethoxy-3-oxo-1-propenyl]-2-isobutoxyphenyl}propanoic acid. After adding 0.12 g of 5% palladium-carbon, the mixture is stirred at ambient temperature for one hour in a stream of hydrogen. The reaction mixture is filtered with Celite, and the solvent is distilled off from the filtrate under a reduced pressure to obtain a crude product. The crude product is dissolved in 4 ml of

ethanol, 0.7 ml of 5 mol/L sodium hydroxide is added, and the mixture thus obtained is stirred at ambient temperature for one hour. Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 5 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced 10 pressure. Thus, 0.53 g of 3-[3-(2-carboxyethyl)-4-isobutoxyphenyl]-3-(2,4-diisobutoxyphenyl)propanoic acid is obtained as a white foaming product.

NMR (CDCl₃) δ: 0.99 (18H,d,J=6.6Hz), 1.80-2.30 (3H,m), 2.44-3.09 (6H,m), 3.66 (6H,d,J=6.4Hz), 4.64-4.91 15 (1H,m), 6.33-6.40 (2H,m), 6.67 (1H,d,J=9.0Hz), 6.91-7.06 (3H,m), 9.90 (2H,brs)

Example 80

In 3 ml of methylene chloride is dissolved 0.12 g of 2-(ethoxycarbonyl)-1-isobutyl-1H-indole-5- 20 carboxylic acid, to which are successively added 50 μl of oxalyl chloride and 20 μl of N,N-dimethylformamide at ambient temperature. The mixture is stirred at ambient temperature for one hour. Then, at 5-10°C, 0.12 g of aluminum chloride and 0.13 g of 1,3- 25 diisobutoxybenzene are successively added and stirred at the same temperature as above for 30 minutes. The reaction mixture is added to a mixture of chloroform

and ice water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 1:1) to obtain 0.18 g of ethyl 5-(2,4-diisobutoxybenzoyl)-1-isobutyl-1H-indole-2-carboxylate as a colorless oily product.

NMR (CDCl₃) δ : 0.57 (6H,d,J=6.6Hz), 0.84-1.10 (12H,m), 1.40 (3H,t,J=7.1Hz), 1.85-2.44 (3H,m), 3.57-3.82 (4H,m), 4.33-4.45 (4H,m), 6.44-6.58 (2H,m), 7.05-8.07 (5H,m)

15 Example 81

The procedure of Example 80 is repeated to obtain ethyl 3-bromo-5-(2,4-diisobutoxybenzoyl)-1-isobutyl-1H-indole-2-carboxylate.

NMR (CDCl₃) δ : 0.56 (6H,d,J=6.6Hz), 0.65-1.58 (16H,m), 1.91-2.36 (2H,m), 3.62 (2H,d,J=6.1Hz), 3.80 (2H,d,J=6.4Hz), 4.23-4.58 (4H,m), 6.30-6.63 (2H,m), 7.31-7.52 (2H,m), 7.90 (1H,dd,J=8.9,2.2Hz), 8.10 (1H,s)

Example 82

In 2 ml of ethanol is dissolved 0.18 g of ethyl 5-(2,4-diisobutoxybenzoyl)-1-isobutyl-1H-indole-2-carboxylate. After adding 0.3 ml of 5 mol/L sodium

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hydroxide, the mixture thus obtained is stirred at ambient temperature for one hour. Water and chloroform are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 1:1). Thus, 0.15 g of 5-(2,4-diisobutoxybenzoyl)-1-isobutyl-1H-indole-2-carboxylic acid is obtained as a white solid product.

NMR (CDCl₃) δ: 0.57 (6H, d, J=6.8Hz), 0.90 (6H, d, J=6.6Hz), 1.06 (6H, d, J=6.6Hz), 1.46-2.40 (3H, m), 3.61 (2H, d, J=6.3Hz), 3.80 (2H, d, J=6.4Hz), 4.43 (2H, d, J=7.3Hz), 6.50-6.63 (2H, m), 7.35-7.52 (4H, m), 7.90 (1H, dd, J=7.8, 1.5Hz), 8.10 (1H, s)

Example 83

The procedure of Example 82 is repeated to obtain 3-bromo-5-(2,4-diisobutoxybenzoyl)-1-isobutyl-1H-indole-2-carboxylic acid.

NMR (CDCl₃) δ: 0.56 (6H, d, J=6.6Hz), 0.88 (6H, d, J=6.6Hz), 1.06 (6H, d, J=6.6Hz), 1.40-1.80 (1H, m), 1.86-2.34 (2H, m), 3.63 (2H, d, J=6.1Hz), 3.80 (2H, d, J=6.3Hz), 4.43 (2H, d, J=7.1Hz), 4.93 (1H, brs), 6.51-6.61 (2H, m), 7.35-7.54 (2H, m), 7.89-8.08 (2H, m)

Example 84

To a solution of 8.0 g of 3-(3-ethoxy-3-oxopropyl)-4-isobutoxybenzoic acid in 80 ml of tetrahydrofuran are dropwise added 3.6 ml of oxalyl chloride and 60 μ l of N,N-dimethylformamide successively, and the mixture thus obtained is stirred at ambient temperature for one hour. Then, to the reaction mixture obtained herein is dropwise added, at -70°C, a pyrrole reagent prepared from 8.5 ml of pyrrole and 82 ml of 1 mol/L solution of methylmagnesium bromide in tetrahydrofuran. After dropping, the temperature is elevated to ambient temperature over a period of one hour, and the mixture is stirred at ambient temperature for one hour. The reaction mixture is cooled with ice water, a saturated aqueous solution of ammonium chloride is dropwise added, the mixture thus obtained is stirred at ambient temperature for 15 minutes, ethyl acetate is added, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 5.0 g of ethyl 3-[2-isobutoxy-5-(1H-pyrrol-2-ylcarbonyl)phenyl]-propanoate as a brown-colored solid product.

NMR (CDCl₃) δ : 1.07 (6H,d,J=6.8Hz), 1.23 (3H,t,J=7.3Hz),

09830559.050701

1.95-2.32 (1H,m), 2.62-2.71 (2H,m), 2.93-3.13 (2H,m),
 3.82 (2H,d,J=6.4Hz), 4.13 (2H,q,J=7.1Hz), 6.25-6.36
 (1H,m), 6.83-6.93 (2H,m), 7.05-7.15 (1H,m), 7.79-7.87
 (2H,m), 9.80 (1H,brs)

5 Example 85

In 10 ml of methylene chloride is dissolved
 1.1 ml of 3-methylbutanoyl chloride, to which is
 dropwise added at 0°C a solution of 1.00 g of ethyl 3-
 [2-isobutoxy-5-(1H-pyrrol-2-ylcarbonyl)phenyl]-
 10 propanoate in 10 ml of methylene chloride. The mixture
 thus obtained is stirred at 0°C for 30 minutes and then
 at ambient temperature for 30 minutes. The reaction
 mixture is added to a mixture of methylene chloride and
 water, and the organic layer is separated. The organic
 15 layer is washed with water and saturated aqueous
 solution of sodium chloride successively and dried over
 anhydrous magnesium sulfate, and the solvent is
 distilled off under reduced pressure. The residue is
 purified by silica gel column chromatography (eluent;
 20 hexane:ethyl acetate = 5:1) to obtain 0.94 g of 2-(3-
 ethoxy-3-oxopropyl)-4-[[4-(3-methylbutanoyl)-1H-pyrrol-
 2-yl]carbonyl]phenyl 3-methylbutanoate as a light
 brown-colored solid product.

NMR (CDCl₃) δ: 0.99 (6H,d,J=6.4Hz), 1.10 (H,d,J=6.4Hz),
 25 1.23 (3H,t,J=7.1Hz), 2.06-3.06 (10H,m), 4.15
 (2H,q,J=7.1Hz), 7.16-7.29 (2H,m), 7.71-7.89 (3H,m),
 10.50 (1H,brs)

09830559 1020701

Example 86

To a solution of 0.9 g of 2-(3-ethoxy-3-oxopropyl)-4-{{[4-(3-methylbutanoyl)-1H-pyrrol-2-yl]carbonyl}phenyl 3-methylbutanoate in 18 ml N,N-

5 dimethylformamide are added 0.12 g of 60% sodium hydride and 0.4 ml of isopentyl iodide successively, and the mixture thus obtained is stirred at 50-60°C for one hour. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6

10 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 0.7 g of

15 2-(3-ethoxy-3-oxopropyl)-4-{{[1-isopentyl-4-(3-methylbutanoyl)-1H-pyrrol-2-yl]carbonyl}phenyl 3-methylbutanoate is obtained as a white solid product.

NMR (CDCl₃) δ: 0.97 (12H,d,J=6.4Hz), 1.09 (6H,d,J=6.3Hz), 1.23 (3H,t,J=7.1Hz), 1.46-1.87 (3H,m),

20 2.09-3.06 (10H,m), 4.13 (2H,q,J=7.1Hz), 4.32-4.50 (2H,m), 7.10-7.21 (2H,m), 7.54-7.76 (3H,m)

Example 87

A solution of 0.68 g of 2-(3-ethoxy-3-oxopropyl)-4-{{[1-isopentyl-4-(3-methylbutanoyl)-1H-

25 pyrrol-2-yl]carbonyl}phenyl 3-methylbutanoate in 4 ml of tetrahydrofuran is dropwise added to a mixture of 14 ml of ethanol and 13 ml of 1 mol/L sodium hydroxide

solution at 40-50°C, and the mixture thus obtained is
 stirred at the same temperature as above for one hour.
 Water and chloroform are added to the reaction mixture,
 pH is adjusted to 2 with 6 mol/L hydrochloric acid, and
 5 the organic layer is separated. The organic layer is
 washed with water and saturated aqueous solution of
 sodium chloride successively and dried over anhydrous
 magnesium sulfate, and the solvent is distilled off
 under reduced pressure. The residue thus obtained is
 10 dissolved in 14 ml of N,N-dimethylformamide, 0.89 g of
 potassium carbonate and 0.9 ml of isopentyl iodide are
 added, and the mixture thus obtained is stirred at 100°C
 for 15 minutes. The reaction mixture cooled to ambient
 temperature is added to a mixture of ethyl acetate and
 15 water, pH is adjusted to 2 with 6 mol/L hydrochloric
 acid, and the organic layer is separated. The organic
 layer is washed with water and saturated aqueous
 solution of sodium chloride and dried over anhydrous
 magnesium sulfate, and the solvent is distilled off
 20 under reduced pressure. The residue is purified by
 silica gel column chromatography (eluent; hexane:ethyl
 acetate = 5:1) to obtain 0.69 g of isopentyl 3-[5-{{1-
 isopentyl-4-(3-methylbutanoyl)-1H-pyrrol-2-
 yl}carbonyl}-2-(isopentyloxy)phenyl]propanoate.
 25 NMR (CDCl₃) δ: 0.86-1.02 (24H,m), 1.45-2.40 (10H,m),
 2.56-2.70 (4H,m) 2.90-3.08 (2H,m), 4.06 (2H,d,J=6.4Hz),
 4.13 (2H,d,J=6.6Hz), 4.38 (2H,t,J=7.2Hz), 6.89
 (1H,d,J=9.3Hz), 7.07 (1H,d,J=1.5Hz), 7.52

090059 050701

(1H,d,J=1.5Hz), 7.69-7.79 (2H,m)

Example 88

To a solution of 0.67 g of isopentyl 3-[5-
 {[1-isopentyl-4-(3-methylbutanoyl)-1H-pyrrol-2-
 5 yl]carbonyl}-2-(isopentyloxy)phenyl]propanoate in 14 ml
 of ethanol is added 3.6 ml of 1 mol/L sodium hydroxide
 solution. The mixture thus obtained is stirred at 50°C
 for one hour. Water and chloroform are added to the
 reaction mixture, pH is adjusted to 2 with 6 mol/L
 10 hydrochloric acid, and the organic layer is separated.
 The organic layer is washed with water and saturated
 aqueous solution of sodium chloride and dried over
 anhydrous magnesium sulfate, and the solvent is
 distilled off under reduced pressure. Thus, 0.56 g of
 15 3-[5- {[1-isopentyl-4-(3-methylbutanoyl)-1H-pyrrol-2-
 yl]carbonyl}-2-(isopentyloxy)phenyl]propanoic acid is
 obtained as a white solid product.

NMR (CDCl₃) δ: 0.97 (18H,d,J=6.1Hz), 1.52-2.41 (7H,m),
 2.58-2.73 (4H,m), 2.94-3.10 (2H,m), 4.09
 20 (2H,t,J=5.6Hz), 4.38 (2H,t,J=6.3Hz), 6.04 (1H,brs),
 6.91 (1H,d,J=8.8Hz), 7.11 (1H,d,J=1.7Hz), 7.47
 (1H,d,J=1.7Hz), 7.69-7.77 (2H,m)

Example 89

To a solution of 0.17 g of 1,3-diisopentyl-2-
 25 oxo-2,3-dihydro-1H-benzimidazole-5-carboxylic acid in 9
 ml of methylene chloride are added 60 µl of oxalyl

chloride and 20 μ l of N,N-dimethylformamide successively. The mixture thus obtained is stirred at ambient temperature for 2 hours. Then, 0.42 g of aluminum chloride and 0.38 g of isopentyl 2-(2-

5 isopentyloxyphenyl)acetate are successively added at ambient temperature, and the mixture thus obtained is stirred at the same temperature as above for 30 minutes. The reaction mixture is added to a mixture of methylene chloride and ice water, and the organic layer

10 is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue is purified by

15 silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 0.29 g of isopentyl 2-[5-[(1,3-diisopentyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)carbonyl]-2-(isopentyloxy)phenyl]acetate as a light yellow oily product.

20 NMR (CDCl_3) δ : 0.87-1.01 (24H,m), 1.31-1.92 (12H,m), 3.65 (2H,s), 3.84-4.20 (8H,m), 6.89-7.05 (2H,m), 7.52-7.81 (4H,m)

Example 90

In a mixture of 3 ml of ethanol and 3 ml of

25 tetrahydrofuran is dissolved 0.28 g of isopentyl 2-[5-[(1,3-diisopentyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)carbonyl]-2-(isopentyloxy)phenyl]acetate. After

adding 1.4 ml of 1 mol/L sodium hydroxide solution, the mixture is stirred at ambient temperature for 3 hours. Water and chloroform are added to the reaction mixture, pH is adjusted to 2 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. Thus, 0.21 g of 2-[5-[(1,3-diisopentyl-2-oxo-2,3-dihydro-1H-benzimidazol-5-yl)carbonyl]-2-(isopentyloxy)phenyl]-acetic acid is obtained as a white foaming product. NMR (CDCl₃) δ: 0.96 (18H,d,J=5.6Hz), 1.38-2.02 (9H,m), 3.71 (2H,s), 3.85-4.16 (6H,m), 6.88-7.81 (7H,m)

Example 91

At ambient temperature, 9.9 ml of iodomethane is dropwise added to a suspension of 50.0 g of 3-[5-(2,4-diisobutoxybenzoyl)-2-isobutoxyphenyl]propanoic acid and 22.0 g of potassium carbonate in 150 ml of N,N-dimethylformamide. The mixture thus obtained is stirred at the same temperature as above for 30 minutes. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and then the solvent

is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 51.0 g of methyl 3-[5-(2,4-diisobutoxybenzoyl)-
 5 2-isobutoxyphenyl]propanoate as a light brown-colored solid product.

NMR (CDCl₃) δ : 0.70 (6H,d,J=6.6Hz), 1.05
 (12H,d,J=6.8Hz), 1.58-2.40 (3H,m), 2.49-3.05 (4H,m),
 3.59-3.82 (6H,m), 3.66 (3H,s), 6.47-6.59 (2H,m), 6.79
 10 (1H,d,J=9.3Hz), 7.35 (1H,d,J=8.1Hz), 7.60-7.68 (2H,m)

Example 92

It is also possible to synthesize the compound 33(6) of Example 33 by the following method.

In 9 ml of methylene chloride is dissolved
 15 0.90 g of 3-(3-ethoxy-3-oxopropyl)-4-isopentyloxybenzoic acid. At ambient temperature, 0.31 ml of oxalyl chloride and 20 μ l of N,N-dimethylformamide are successively added and the mixture thus obtained is stirred at ambient temperature
 20 for one hour. Then, at 5-10°C, 0.78 g of aluminum chloride and 0.78 g of 1,3-diisobutoxybenzene are successively added. The mixture thus obtained is stirred first at the same temperature as above for 30 minutes and then at ambient temperature for 30 minutes.
 25 Further, 0.39 g of aluminum chloride is added at ambient temperature and stirred at the same temperature as above for 30 minutes. The reaction mixture is added

to a mixture of chloroform and ice water and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over
5 anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to obtain 0.67 g of ethyl 3-[5-(2-hydroxy-4-
10 isobutoxybenzoyl)-2-isopentyloxyphenyl]propanoate as a light yellow oily product.

Example 93

In 10 ml of methylene chloride is dissolved 1.00 g of 3-(3-ethoxy-3-oxopropyl)-4-isobutoxybenzoic
15 acid. After adding 0.36 ml of oxalyl chloride and 20 μ l of N,N-dimethylformamide successively at ambient temperature, the mixture thus obtained is stirred at ambient temperature for one hour. Then, 0.95 g of aluminum chloride and 1.02 g of 1,3-
20 diisopentyloxybenzene are successively added at 5-10°C, and stirred at the same temperature as above for 30 minutes and then at ambient temperature for 30 minutes. Then, 0.45 g of aluminum chloride is added at ambient temperature and stirred at the same temperature as
25 above for 30 minutes. The reaction mixture is added to a mixture of methylene chloride and water, and the organic layer is separated. The organic layer thus

obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to obtain 0.63 g of ethyl 3-[5-(2-hydroxy-4-isopentyloxybenzoyl)-2-isobutoxyphenyl]propanoate as a light yellow oily product. A 0.60 g portion of the oily product obtained above is dissolved in 12 ml of ethanol, 1.3 ml of 5 mol/L sodium hydroxide solution is added, and the mixture thus obtained is stirred at ambient temperature for 2 hours. Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.48 g of [5-(2-hydroxy-4-isopentyloxybenzoyl)-2-isobutoxyphenyl]-propanoic acid is obtained as a light yellow solid product.

NMR (CDCl₃) δ : 0.96 (6H,d,J=6.1Hz), 1.07 (6H,d,J=6.6Hz), 1.59-2.32 (4H,m), 2.66-3.11 (4H,m), 3.82 (2H,d,J=6.1Hz), 4.04 (2H,t,J=6.1Hz), 6.33-6.62 (2H,m), 6.89 (1H,d,J=9.0Hz), 7.48-7.57 (3H,m), 8.70 (1H,brs), 12.67 (1H,s)

Referential Example 1

In 100 ml of tetrahydrofuran is suspended 39.8 g of isopentyltriphenylphosphonium iodide. At -25°C to -20°C, 52 ml of a 1.6 mol/L solution of n-butyllithium in n-hexane is dropwise added to the suspension. After stirring the mixture thus obtained at -25°C to -15°C for one hour, the temperature is elevated to ambient temperature over a period of one hour. A solution of 10.0 g of 1,4-dioxaspiro[4.5]-decan-8-one in 50 ml of tetrahydrofuran is added to the reaction mixture and stirred at ambient temperature for one hour. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 95:5) to obtain 10.5 g of 8-(3-methylbutylidene)-1,4-dioxaspiro[4.5]decane as a colorless oily product.

NMR (CDCl₃) δ: 0.87 (6H,d,J=6.3Hz), 1.1-2.4 (11H,m), 3.96 (2H,s), 3.97 (2H,s), 5.16 (1H,t,J=7.4Hz)

Referential Example 2

In 50 ml of tetrahydrofuran is dissolved 10.0 g of 8-(3-methylbutylidene)-1,4-dioxaspiro[4.5]decane.

After adding 50 ml of 6 mol/L hydrochloric acid, the mixture thus obtained is stirred at ambient temperature for one hour. Chloroform and water are added to the reaction mixture and the organic layer is separated.

- 5 The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is
- 10 purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 98:2) to obtain 6.6 g of 4-(3-methylbutylidene)-1-cyclohexanone as a colorless oily product.

NMR (CDCl₃) δ: 0.91 (6H,d,J=6.4Hz), 1.2-2.8 (11H,m),
15 5.37 (1H,t,J=7.3Hz)

Referential Example 3

- In a mixture of 3.5 ml of ethanol and 1.5 ml of water are dissolved 1.0 g of 4-(3-methylbutylidene)-1-cyclohexanone, 1.1 g of D-cysteine hydrochloride
- 20 monohydrate and 0.52 g of sodium acetate. The resulting solution is stirred at ambient temperature for 2 hours. Water is added to the reaction mixture and the deposited crystal is collected by filtration. Thus, 0.81 g of (3S)-8-(3-methylbutylidene)-1-thia-4-
- 25 azaspiro[4.5]decane-3-carboxylic acid is obtained as a colorless crystalline product.

NMR (CDCl₃) δ: 0.87 (6H,d,J=6.1Hz), 1.2-2.8 (11H,m),

3.1-3.6 (2H,m), 4.34 (1H,t,J=7.8Hz), 5.19
(1H,t,J=7.1Hz), 6.9-7.5 (2H,bs)

Referential Example 4

In 100 ml of N,N-dimethylformamide are
5 dissolved 10.0 g of methyl salicylate, 18.1 g of
potassium carbonate and 11.3 ml of isobutyl iodide.
The solution is heated under reflux for 1.5 hours with
stirring. The reaction mixture is added to a mixture
of ethyl acetate and water, pH is adjusted to 2.0 with
10 6 mol/L hydrochloric acid, and the organic layer is
separated. The organic layer thus obtained is washed
with water and saturated aqueous solution of sodium
chloride successively and dried over anhydrous
magnesium sulfate, and then the solvent is distilled
15 off under reduced pressure. The residue thus obtained
is purified by silica gel column chromatography
(eluent; n-hexane:ethyl acetate = 95:5) to obtain 4.2 g
of methyl 2-isobutoxybenzoate as a light yellow oily
product.
20 NMR (CDCl₃) δ: 1.06 (6H,d,J=6.6Hz), 1.8-2.4 (1H,m), 3.79
(2H,d,J=6.4Hz), 3.98 (3H,s), 6.8-7.1 (2H,m), 7.3-7.6
(1H,m), 7.7-7.9 (1H,m)

Referential Example 5

In 20 ml of methanol is dissolved 4.1 g of
25 methyl 2-isobutoxybenzoate. After adding 6 ml of 5
mol/L solution of sodium hydroxide, the mixture thus

obtained is stirred at ambient temperature for 2 hours. Ethyl acetate and water are added to the reaction mixture, pH is adjusted to 2 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 3.9 g of 2-isobutoxybenzoic acid is obtained as a colorless crystalline product.

Referential Example 6

In 40 ml of methylene chloride are dissolved 3.8 g of 2-isobutoxybenzoic acid and 2.8 ml of thionyl chloride. The solution is heated under reflux for one hour with stirring. The reaction mixture obtained herein is dropwise added at 5-10°C to a solution of diazomethane in ethyl ether prepared from 53.0 g of N-methylnitrosourea, 83.0 g of potassium hydroxide, 120 ml of water and 150 ml of ethyl ether, and the mixture thus obtained is stirred at ambient temperature for 2 hours. Ethyl ether, acetic acid and water are added to the reaction mixture, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained

is dissolved in 30 ml of methanol, and the resulting solution is added to a mixture of 2.3 g of silver benzoate and 23 ml of triethylamine at 25-30°C, and stirred for 1.5 hours. Ethyl acetate and water are added to the reaction mixture, pH is adjusted to 2.0 with concentrated hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 9:1) to obtain 3.8 g of methyl 2-(2-isobutoxyphenyl)acetate as a colorless oily product.

NMR (CDCl₃) δ : 1.02 (6H,d,J=6.8Hz), 1.8-2.4 (1H,m), 3.5-3.9 (7H,m), 6.7-7.1 (2H,m), 7.1-7.4 (2H,m)

Referential Example 7

In 10 ml of methylene chloride is dissolved 1.00 g of methyl 2-(2-isobutoxyphenyl)acetate. After successively adding 0.99 ml of titanium tetrachloride and 0.45 ml of α,α -dichloromethyl methyl ether at 5-10°C, the mixture thus obtained is stirred at ambient temperature for 30 minutes. The reaction mixture is added to a mixture of methylene chloride and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous

solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue is purified by silica gel column chromatography (eluent; 5 n-hexane:ethyl acetate = 95:5) to obtain 0.80 g of methyl 2-(5-formyl-2-isobutoxyphenyl)acetate as a colorless oily product.

NMR (CDCl₃) δ: 1.03 (6H,d,J=6.8Hz), 1.8-2.4 (1H,m), 3.69 (5H,s), 3.83 (2H,d,J=6.4Hz), 6.95 (1H,d,J=8.3Hz), 7.6-10 7.9 (2H,m), 9.86 (1H,s)

Referential Example 8

In 8 ml of acetonitrile is dissolved 0.80 g of methyl 2-(5-formyl-2-isobutoxyphenyl)acetate. After successively adding 2.03 g of sodium dihydrogen-15 phosphate dissolved in 25 ml of water, 0.69 ml of 30% aqueous hydrogen peroxide and 0.73 g of sodium chlorite dissolved in 15 ml of water at a temperature of 5-10°C, the mixture thus obtained is stirred at 5-10°C for 3.5 hours. Chloroform and water are added to the reaction20 mixture, pH is adjusted to 2.0 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium25 sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.62 g of 3-(methoxycarbonylmethyl)-4-isobutoxybenzoic acid is

obtained as a colorless crystalline product.

NMR (CDCl₃) δ : 1.03 (6H,d,J=6.6Hz), 1.8-2.4 (1H,m), 3.69 (5H,s), 3.81 (2H,d,J=6.4Hz), 6.89 (1H,d,J=8.3Hz), 7.8-8.2 (2H,m), 8.8-9.6 (1H,bs)

5 Referential Example 9

In a mixture of 10 ml of pyridine and 10 ml of water is dissolved 0.50 g of isobutyl 2-isobutoxy-5-methylbenzoate. After adding 0.45 g of potassium permanganate at 60-70°C, the mixture thus obtained is heated under reflux for 2 hours with stirring. The reaction mixture is filtered with Celite, ethyl acetate is added to the filtrate, pH is adjusted to 2.0 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.35 g of 3-(isobutoxycarbonyl)-4-isobutoxybenzoic acid is obtained as a colorless crystalline product.

NMR (CDCl₃) δ : 1.02 (6H,d,J=6.4Hz), 1.07 (6H,d,J=6.4Hz), 1.9-2.4 (2H,m), 3.88 (2H,d,J=6.4Hz), 4.12 (2H,d,J=6.8Hz), 7.00 (1H,d,J=9.0Hz), 8.19 (1H,dd,J=8.7,2.2Hz), 8.54 (1H,d,J=2.2Hz), 7.0-9.0 (1H,bs)

Referential Example 10

In 700 ml of N,N-dimethylformamide are dissolved 70.0 g of salicylaldehyde and 158.5 g of potassium carbonate. After dropwise adding 67.9 ml of 3-chloro-2-methyl-1-propene at 70°C over a period of 30 minutes, the mixture thus obtained is stirred at 70°C for 30 minutes. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 3.0 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is successively washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is dissolved in 350 ml of ethanol, 7.0 g of 5% palladium-carbon is added, and the mixture is stirred at 35°C for 4 hours in a stream of hydrogen. The reaction mixture is filtered with Celite, the solvent is distilled off from the filtrate under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:toluene = 2:1) to obtain 92.4 g of 2-isobutoxybenzaldehyde as a light yellow oily product.

NMR (CDCl₃) δ: 1.07 (6H,d,J=6.6Hz), 2.0-2.2 (1H,m), 3.85 (2H,d,J=6.4Hz), 6.9-7.1 (2H,m), 7.4-7.7 (1H,m), 7.83 (1H,dd,J=8.1,2.0Hz), 10.55 (1H,s)

Example 11

In 30 ml of tetrahydrofuran is suspended 0.92 g of 60% sodium hydride. After dropping 5.0 ml of ethyl diethylphosphonoacetate thereinto at ambient temperature over a period of 5 minutes, the mixture thus obtained is stirred at 40°C for 30 minutes. Then, a solution of 3.40 g of 2-isobutoxybenzaldehyde in 20 ml of tetrahydrofuran is dropwise added at ambient temperature over a period of 20 minutes, and the mixture thus obtained is stirred for one hour. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 9:1) to obtain 4.30 g of ethyl 3-(2-isobutoxyphenyl)-2-propenoate as a light yellow oily product.

NMR (CDCl₃) δ: 1.06 (6H,d,J=6.6Hz), 1.32 (3H,t,J=7.1Hz), 1.8-2.4 (1H,m), 3.78 (2H,d,J=6.4Hz), 4.25 (2H,q,J=7.1Hz), 6.53 (1H,d,J=16.4Hz), 6.8-7.6 (4H,m), 8.10 (1H,d,J=16.1Hz)

25 Referential Example 12

In 15 ml of ethanol is dissolved 1.50 g of ethyl 3-(2-isobutoxyphenyl)-2-propenoate, to which is

added 0.30 g of 5% palladium-carbon. The mixture is stirred at ambient temperature for one hour in a stream of hydrogen. The reaction mixture is filtered with Celite, and the solvent is distilled off from the filtrate under reduced pressure. The residue thus obtained is purified by silica gel column chromatography to obtain 0.76 g of ethyl 3-(2-isobutoxyphenyl)propionate as a colorless oily product. NMR (CDCl₃) δ: 1.04 (6H,d,J=6.6Hz), 1.22 (3H,t,J=7.1Hz), 1.9-2.3 (1H,m), 2.5-2.7 (2H,m), 2.9-3.1 (2H,m), 3.73 (2H,d,J=6.4Hz), 4.12 (2H,q,J=6.8Hz), 6.7-7.3 (4H,m)

Referential Example 13

The procedure of referential Example 7 is repeated to obtain ethyl 3-(5-formyl-2-isobutoxyphenyl)propionate. NMR (CDCl₃) δ: 1.07 (6H,d,J=6.6Hz), 1.23 (3H,t,J=7.1Hz), 2.0-2.4 (1H,m), 2.5-2.8 (2H,m), 2.9-3.1 (2H,m), 3.84 (2H,d,J=6.4Hz), 4.13 (2H,d,J=7.1Hz), 6.93 (1H,d,J=9.0Hz), 7.7-7.9 (2H,m), 9.85 (1H,s)

Referential Example 14

The procedure of Referential Example 7 is repeated to obtain ethyl 3-(5-formyl-2-isobutoxyphenyl)-2-propenoate. NMR (CDCl₃) δ: 1.09 (6H,d,J=6.6Hz), 1.34 (3H,t,J=7.1Hz), 2.0-2.5 (1H,m), 3.90 (2H,d,J=6.3Hz), 4.28 (2H,q,J=7.1Hz), 6.61 (1H,d,J=16.1Hz), 7.02

Referential Example 15

5 isobutoxybenzoic acid.

10 Example 16

15 1.9-2.4 (1H,m), 3.89 (2H,d,J=6.4Hz), 4.28

Referential Example 17

In 59 ml of methylene chloride are dissolved
20 11.8 g of 1-benzyl 2-ethyl (2S,4R)-4-hydroxy-1,2-
pyrrolidinedicarboxylate, 11 ml of 3,4-dihydropyran
and 2.0 g of pyridinium p-toluenesulfonate. The
solution is heated under reflux for one hour. The
reaction mixture is added to 50 ml of saturated aqueous
25 solution of sodium bicarbonate, and the organic layer

is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under
5 reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 2:1) to obtain 12.9 g of 1-benzyl 2-ethyl (2S,4R)-4-(tetrahydro-2H-pyran-2-yloxy)-1,2-pyrrolidinedicarboxylate as a colorless oily
10 product.

NMR (CDCl₃) δ : 1.0-2.6 (11H,m), 3.3-4.7 (9H,m), 4.9-5.3 (2H,m), 7.1-7.5 (5H,m)

Referential Example 18

In 127 ml of ethanol is dissolved 12.7 g of
15 1-benzyl 2-ethyl (2S,4R)-4-(tetrahydro-2H-pyran-2-yloxy)-1,2-pyrrolidinedicarboxylate. After adding 37.0 ml of 1 mol/L sodium hydroxide solution at 5-10°C, the mixture thus obtained is stirred at ambient temperature for 1.5 hours. The solvent is distilled off from the
20 reaction mixture under reduce pressure, the residue thus obtained is dissolved in 90 ml of N,N-dimethylformamide, 10.9 ml of diphenylphosphoryl azide, 14.1 ml of triethylamine and 3.94 g of N,O-dimethylhydroxylamine hydrochloride are successively
25 added at 5-10°C, and the mixture thus obtained is stirred at ambient temperature for one hour. Ethyl acetate and water are added to the reaction mixture, pH

is adjusted to 6.5 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous sodium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 4:1) to obtain 3.75 g of benzyl (2S,4R)-2-{[methoxy(methyl)amino]carbonyl}-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate as a light yellow oily product.

NMR (CDCl₃) δ: 1.2-2.6 (8H,m), 3.0-4.0 (10H,m), 4.3-5.3 (5H,m), 7.2-7.5 (5H,m)

Referential Example 19

In 33 ml of tetrahydrofuran is dissolved 3.3 g of benzyl (2S,4R)-2-{[methoxy(methyl)amino]carbonyl}-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate. After adding 0.64 g of lithium aluminum hydride at -70°C, the mixture thus obtained is stirred at -70°C for one hour. After dropwise adding 33 ml of ethyl acetate to the reaction mixture over a period of 30 minutes and then 66 ml of tetrahydrofuran containing 20% of water over a period of 30 minutes, the mixture thus obtained is stirred at ambient temperature for 30 minutes. The mixture is filtered with Celite, and the organic layer is separated from the filtrate. The organic layer is washed with water and saturated

aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 1:1) to obtain 1.25 g of benzyl (2S,4R)-2-formyl-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate as a light yellow oily product.

NMR (CDCl₃) δ: 1.2-2.5 (8H,m), 3.3-4.0 (4H,m), 4.1-4.8 (3H,m), 5.17 (2H,bs), 7.1-7.5 (5H,m), 9.4-9.7 (1H,m)

Referential Example 20

In 11 ml of tetrahydrofuran is suspended 3.34 g of isopentyltriphenylphosphonium iodide, to which is dropwise added 4.3 ml of a 1.53 mol/L solution of n-butyllithium in n-hexane at -25°C to -20°C. After stirring the mixture at -25°C to -15°C for one hour, the temperature is elevated to ambient temperature in one hour. To the reaction mixture is dropwise added 1.10 g of benzyl (2S,4R)-2-formyl-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate dissolved in 11 ml of tetrahydrofuran over a period of 20 minutes. The mixture thus obtained is stirred at ambient temperature for 5 hours. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous

magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 4:1) to obtain 0.62 g of benzyl (2S,4R)-2-(4-methyl-1-pentenyl)-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate as a light yellow oily product.

NMR (CDCl₃) δ: 0.85 (6H,d,J=6.1Hz), 1.3-2.5 (11H,m), 3.3-4.0 (4H,m), 4.2-4.9 (3H,m), 5.10 (2H,bs), 5.2-5.6 (2H,m), 7.32 (5H,bs)

Referential Example 21

In 12 ml of tetrahydrofuran is dissolved 0.60 g of benzyl (2S,4R)-2-(4-methyl-1-pentenyl)-4-(tetrahydro-2H-pyran-2-yloxy)-1-pyrrolidinecarboxylate, to which is added 12 ml of 6 mol/L hydrochloric acid. The mixture thus obtained is stirred at ambient temperature for 2 hours. A mixture of chloroform and water is added to the reaction mixture, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; n-hexane:ethyl acetate = 2:1) to obtain 0.43 g of benzyl (2S,4R)-4-hydroxy-2-(4-methyl-1-pentenyl)-1-pyrrolidinecarboxylate as a light yellow oily product.

NMR (CDCl₃) δ: 0.85 (6H,d,J=5.9Hz), 1.2-2.4 (5H,m), 3.4-3.9 (2H,m), 4.3-4.6 (1H,m), 4.6-5.0 (2H,m), 5.10 (2H,bs), 5.2-5.7 (2H,m), 7.2-7.5 (5H,m)

Referential Example 22

- 5 After adding 0.04 g of tetrabutylammonium
bromide to 8 ml of 50% aqueous solution of sodium
hydroxide, the mixture is heated to 120°C. Thereto is
dropwise added a solution of 0.40 g of benzyl (2S,4R)-
4-hydroxy-2-(4-methyl-1-pentenyl)-1-
10 pyrrolidinecarboxylate and 0.65 ml of 3-chloro-2-
methyl-1-propene in 0.8 ml of toluene over a period of
5 minutes. The mixture thus obtained is heated under
reflux for 30 minutes with stirring. The reaction
mixture is cooled to ambient temperature, toluene and
15 water are added, and the organic layer is separated.
The organic layer thus obtained is washed with water
and saturated aqueous solution of sodium chloride
successively and dried over anhydrous magnesium
sulfate, and then the solvent is distilled off under
20 reduced pressure. The residue thus obtained is
purified by silica gel column chromatography (eluent;
n-hexane:ethyl acetate = 10:1) to obtain 0.31 g of
benzyl (2S,4R)-2-(4-methyl-1-pentenyl)-4-[(2-methyl-2-
propenyl)oxy]-1-pyrrolidinecarboxylate as a colorless
25 oily product.
- NMR (CDCl₃) δ: 0.84 (6H,d,J=5.9Hz), 1.2-2.5 (8H,m), 3.3-4.1 (5H,m), 4.6-5.6 (7H,m), 7.32 (5H,bs)

Referential Example 23

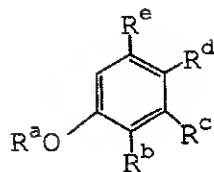
In 5.8 ml of ethanol is dissolved 0.29 g of
benzyl (2S,4R)-2-(4-methyl-1-pentenyl)-4-[(2-methyl-2-
propenyl)oxy]-1-pyrrolidinecarboxylate. After adding
5 0.06 g of 5% palladium-carbon, the mixture is stirred
at ambient temperature for 1.5 hours in a stream of
hydrogen. The reaction mixture is filtered with
Celite, and the solvent is distilled off from the
filtrate under reduced pressure. Thus, 0.18 g of
10 (2R,4R)-4-isobutoxy-2-(4-methylpentyl)-pyrrolidine is
obtained as a yellow oily product.
NMR (CDCl₃) δ: 0.86 (6H,d,J=6.1Hz), 0.89 (6H,d,J=6.6Hz),
1.0-2.2 (11H,m), 2.7-3.4 (5H,m), 3.8-4.1 (1H,m)

Example 24

15 The procedure of Referential Example 4 is
repeated to obtain the compounds shown in Table 88.

102090-6907360

[Table 88]



No.	R ^a	R ^b	R ^c	R ^d	R ^e
24 (1)	nPr	CHO	H	H	H
24 (2)	iAm	CHO	H	H	H
24 (3)	iBu	COOMe	H	H	OCH ₂ Ph
24 (4)	iBu	COO-iBu	H	Me	H
24 (5)	iBu	Me	H	H	COO-iBu
24 (6)	CH ₂ Ph	H	OH	COOMe	H
24 (7)	(4-NO ₂) PhCH ₂	(CH ₂) ₂ COOEt	H	H	H
24 (8)	iBu	(CH ₂) ₂ COO-iBu	H	H	H
24 (9)	iAm	CH ₂ COO-iAm	H	H	H

24 (1)

NMR (CDCl₃) δ: 1.07 (3H, t, J=7.3Hz), 1.65-2.07 (2H, m),
4.04 (2H, t, J=6.3Hz), 7.00 (2H, t, J=7.3Hz), 7.43-7.63
(1H, m), 7.83 (1H, dd, J=8.1, 2.2Hz), 10.53 (1H, d, J=0.7Hz)

5 24 (2)

NMR (CDCl₃) δ: 0.98 (6H, d, J=5.9Hz), 1.64-2.03 (3H, m),
4.11 (2H, t, J=6.4Hz), 6.92-7.08 (2H, m), 7.43-7.63
(1H, m), 7.83 (1H, dd, J=7.7, 2.0Hz), 10.52 (1H, s)

24 (3)

10 NMR (CDCl₃) δ: 1.06 (6H, d, J=6.6Hz), 2.07-2.36 (1H, m),
3.75 (2H, d, J=6.4Hz), 3.85 (3H, s), 5.09 (2H, s), 6.48-
6.61 (2H, m), 7.31-7.47 (5H, m), 7.84 (1H, d, J=9.3Hz)

24 (4)

NMR (CDCl₃) δ : 1.00 (6H,d,J=6.8Hz), 1.03 (6H,d,J=6.6Hz),
2.00-2.19 (2H,m), 2.28 (3H,s), 3.75 (2H,d,J=6.4Hz),
4.08 (2H,d,J=6.6Hz), 6.82 (1H,d,J=8.5Hz), 7.20
(1H,dd,J=8.5,2.4Hz), 7.57 (1H,d,J=2.4Hz)

5 24(5)

NMR (CDCl₃) δ : 1.02 (6H,d,J=6.6Hz), 1.06 (6H,d,J=6.6Hz),
1.88-2.41 (2H,m), 2.28 (3H,s), 3.79 (2H,d,J=6.4Hz),
4.09 (2H,d,J=6.6Hz), 7.17 (1H,d,J=8.1Hz), 7.47-7.59
(2H,m)

10 24(6)

NMR (CDCl₃) δ : 3.91 (3H,s), 5.07 (2H,s), 6.44-6.58
(2H,m), 7.25-7.40 (5H,s), 7.74 (1H,d,J=9.5Hz), 10.96
(1H,s)

24(7)

15 NMR (CDCl₃) δ : 1.23 (3H,t,J=7.1Hz), 2.53-2.71 (2H,m),
2.94-3.12 (2H,m), 4.12 (2H,q,J=7.1Hz), 5.20 (2H,s),
6.79-7.09 (2H,m), 7.11-7.25 (2H,m), 7.61
(2H,d,J=8.6Hz), 8.26 (2H,d,J=8.6Hz)

24(8)

20 NMR (CDCl₃) δ : 0.90 (6H,d,J=6.6Hz), 1.05 (6H,d,J=6.6Hz),
1.67-2.26 (2H,m), 2.51-3.04 (4H,m), 3.73
(2H,d,J=6.4Hz), 3.85 (2H,d,J=6.6Hz), 6.74-6.91 (2H,m),
7.09-7.25 (2H,m)

24(9)

25 NMR (CDCl₃) δ : 0.89 (6H,d,J=5.6Hz), 0.95 (6H,d,J=5.6Hz),
1.40-1.94 (6H,m), 3.60 (2H,s), 3.98 (2H,t,J=6.1Hz),
4.11 (2H,t,J=5.9Hz), 6.80-6.95 (2H,m), 7.14-7.35 (2H,m)

Referential Example 25

Isobutyl 2-fluoro-4-isobutoxybenzoate is treated in the same manner as in Referential Example 5 to obtain 2-fluoro-4-isobutoxybenzoic acid.

NMR (CDCl₃) δ: 1.03 (6H,d,J=6.6Hz), 1.90-2.41 (1H,m),
5 3.77 (2H,d,J=6.6Hz), 6.56-6.80 (2H,m), 7.97
(1H,dd,J=9.0,8.6Hz), 9.10 (1H,brs)

Referential Example 26

The procedure of Referential Example 6 is repeated to obtain methyl 2-(2-propoxyphenyl)acetate.

10 NMR (CDCl₃) δ: 1.02 (3H,t,J=7.2Hz), 1.58-1.96 (2H,m),
3.63 (2H,s), 3.68 (3H,s), 3.92 (2H,t,J=6.4Hz), 6.88
(2H,t,J=6.4Hz), 7.14-7.33 (2H,m)

Referential Example 27

The procedure of Referential Example 6 is repeated to obtain methyl 2-(2-isopentyloxyphenyl)-
15 acetate.

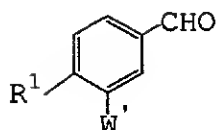
NMR (CDCl₃) δ: 0.95 (6H,d,J=7.1Hz), 1.56-1.90 (3H,m),
3.63 (2H,s), 3.68 (3H,s), 3.99 (2H,t,J=6.3Hz), 6.84
(2H,t,J=7.3Hz), 7.15-7.32 (2H,m)

20 Referential Example 28

The procedure of Referential Example 7 is repeated to obtain the compounds shown in Table 89.

0930559-05070

[Table 89]



No.	R ¹	W'
28 (1)	O-nPr	CH ₂ COOMe
28 (2)	O-iAm	CH ₂ COOMe
28 (3)	O-iAm	(CH ₂) ₂ COOEt
28 (4)	(4-NO ₂) PhCH ₂ -O-	(CH ₂) ₂ COOEt
28 (5)	O-iBu	(CH ₂) ₃ COOEt
28 (6)	O-iBu	CH ₂ CH=CHCOOEt
28 (7)	O-iAm	CH ₂ CH=CHCOOEt

28 (1)

NMR (CDCl₃) δ: 1.04 (3H, t, J=7.3Hz), 1.63-1.94 (2H, m),
3.68 (2H, s), 3.70 (3H, s), 4.03 (2H, t, J=6.3Hz), 6.96
(1H, d, J=8.1Hz), 7.74-7.86 (2H, m), 9.87 (1H, s)

5 28 (2)

NMR (CDCl₃) δ: 0.97 (6H, d, J=6.1Hz), 1.65-1.84 (3H, m),
3.67 (2H, s), 3.69 (3H, s), 4.10 (2H, t, J=6.2Hz), 6.98
(1H, d, J=8.0Hz), 7.74-7.86 (2H, m), 9.87 (1H, s)

28 (3)

10 NMR (CDCl₃) δ: 0.99 (6H, d, J=6.1Hz), 1.23 (3H, t, J=7.1Hz),
1.59-2.04 (3H, m), 2.51-2.70 (2H, m), 2.89-3.06 (2H, m),
4.01-4.25 (4H, m), 6.94 (1H, d, J=9.3Hz), 7.69-7.80
(2H, m), 9.85 (1H, s)

28 (4)

NMR (CDCl₃) δ : 1.23 (3H,t,J=7.1Hz), 2.58-2.76 (2H,m),
3.00-3.18 (2H,m), 4.12 (2H,q,J=7.1Hz), 5.32 (2H,s),
6.99 (1H,d,J=9.0Hz), 7.59-7.78 (4H,m), 8.27
(2H,d,J=8.8Hz), 9.88 (1H,s)

5 28(5)

NMR (CDCl₃) δ : 1.07 (6H,d,J=6.8Hz), 1.25 (3H,t,J=7.1Hz),
1.85-2.16 (3H,m), 2.35 (2H,t,J=6.8Hz), 2.73
(2H,t,J=6.8Hz), 3.83 (2H,d,J=6.4Hz), 4.12
(2H,q,J=7.1Hz), 6.92 (1H,d,J=9.0Hz), 7.67-7.77 (2H,m),

10 9.86 (1H,s)

28(6)

NMR (CDCl₃) δ : 1.05 (6H,d,J=6.3Hz), 1.27 (3H,t,J=7.1Hz),
2.07-2.28 (1H,m), 3.58 (2H,d,J=6.6Hz), 3.84
(2H,d,J=6.4Hz), 4.19 (2H,q,J=7.1Hz), 5.80

15 (1H,d,J=15.6Hz), 6.91-7.19 (2H,m), 7.68-7.82 (2H,m),
9.86 (1H,s)

28(7)

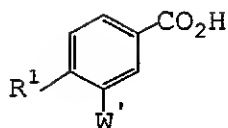
NMR (CDCl₃) δ : 0.97 (6H,d,J=5.9Hz), 1.27 (3H,t,J=7.2Hz),
1.65-1.96 (3H,m), 3.55 (2H,d,J=6.8Hz), 4.03-4.29

20 (4H,m), 5.79 (1H,dt,J=15.6,1.5Hz), 6.92-7.30 (2H,m),
7.67-7.80 (2H,m), 9.86 (1H,d,J=1.0Hz)

Referential Example 29

The procedure of Referential Example 8 is repeated to obtain the compounds shown in Table 90.

[Table 90]



No.	R ¹	W'
29 (1)	O-nPr	CH ₂ COOMe
29 (2)	O-iAm	CH ₂ COOMe
29 (3)	O-iAm	(CH ₂) ₂ COOEt
29 (4)	(4-NO ₂) PhCH ₂ -O-	(CH ₂) ₂ COOEt
29 (5)	O-iBu	(CH ₂) ₃ COOEt
29 (6)	O-iBu	CH ₂ CH=CHCOOEt
29 (7)	O-iAm	CH ₂ CH=CHCOOEt

29 (1)

NMR (CDCl₃) δ: 1.04 (3H,t,J=7.4Hz), 1.65-2.03 (2H,m),
3.67 (2H,s), 3.70 (3H,s), 4.01 (2H,t,J=6.4Hz), 7.00
(1H,d,J=8.4Hz), 7.93-8.10 (2H,m), 8.60 (1H,brs)

5 29 (2)

NMR (CDCl₃) δ: 0.96 (6H,d,J=5.9Hz), 1.56-1.99 (3H,m),
3.66 (2H,s), 3.69 (3H,s), 4.17 (2H,t,J=6.3Hz), 6.90
(1H,d,J=8.4Hz), 7.93-8.11 (2H,m), 11.63 (1H,brs)

29 (3)

10 NMR (CDCl₃) δ: 0.98 (6H,d,J=6.0Hz), 1.25 (3H,t,J=7.1Hz),
1.60-2.05 (3H,m), 2.51-2.69 (2H,m), 2.89-3.05 (2H,m),
4.01-4.26 (4H,m), 5.70 (1H,brs), 6.88 (1H,d,J=8.3Hz),
7.92-8.03 (2H,m)

29 (4)

NMR (CDCl₃) δ : 1.22 (3H,t,J=7.1Hz), 2.56-2.71 (2H,m),
2.96-3.04 (2H,m), 4.10 (2H,q,J=7.1Hz), 5.32 (2H,s),
6.94 (1H,d,J=9.0Hz), 7.64-7.92 (5H,m), 8.27
(2H,d,J=8.1Hz)

5 29(5)

NMR (CDCl₃) δ : 1.06 (6H,d,J=6.6Hz), 1.25 (3H,t,J=7.1Hz),
1.95-2.10 (3H,m), 2.34 (2H,t,J=6.6Hz), 2.72
(2H,t,J=7.1Hz), 3.80 (2H,d,J=6.4Hz), 4.12
(2H,q,J=7.1Hz), 6.85 (1H,d,J=8.3Hz), 7.90-8.00 (2H,m),

10 12.00 (1H,brs)

29(6)

NMR (CDCl₃) δ : 1.05 (6H,d,J=6.6Hz), 1.27 (3H,t,J=7.1Hz),
2.00-2.25 (1H,m), 3.56 (2H,d,J=6.6Hz), 3.82
(2H,d,J=6.3Hz), 4.17 (2H,q,J=7.1Hz), 5.79

15 (1H,d,J=15.6Hz), 6.83-7.20 (2H,m), 7.87-8.07 (2H,m),
11.30 (1H,brs)

29(7)

NMR (CDCl₃) δ : 0.97 (6H,d,J=5.9Hz), 1.27 (3H,t,J=7.1Hz),
1.63-2.00 (3H,m), 3.53 (2H,d,J=6.6Hz), 3.88-4.30

20 (4H,m), 5.79 (1H,d,J=15.6Hz), 6.85-7.18 (2H,m), 7.86-
8.07 (2H,m), 9.45 (1H,brs)

Referential Example 30

The procedure of Referential Example 9 is
repeated to obtain 2-isobutoxy-4-(isobutoxycarbonyl)-
25 benzoic acid.

NMR (CDCl₃) δ : 1.04 (6H,d,J=7.3Hz), 1.12 (6H,d,J=6.8Hz),
1.89-2.49 (2H,m), 4.10 (2H,d,J=6.4Hz), 4.15

(2H,d,J=6.3Hz), 7.71-7.81 (3H,m), 8.26 (1H,d,J=7.6Hz)

Referential Example 31

In 200 ml of tetrahydrofuran are suspended 144 g of (methoxymethyl)triphenylphosphonium chloride and 43 g of diisopropylamine, to which is dropwise added 253 ml of a 1.6 mol/L solution of n-butyllithium in hexane at -50°C over a period of one hour. The mixture thus obtained is stirred at ambient temperature for one hour. Then, a solution of 25 g of 2-isobutoxybenzaldehyde in 100 ml of tetrahydrofuran is dropwise added to the reaction mixture obtained above at -50°C over a period of one hour, and the mixture thus obtained is stirred at ambient temperature for one hour. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue obtained above is mixed with 260 ml of 5% aqueous solution of sulfuric acid and 100 ml of dioxane, heated under reflux for 2 hours, cooled to ambient temperature and diluted with 500 ml of water. Ethyl acetate is added to the reaction mixture and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and

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dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 95:5) to
 5 obtain 17.5 g of 2-(2-isobutoxyphenyl)ethanal as a colorless oily product.

NMR (CDCl₃) δ: 1.02 (6H,d,J=6.8Hz), 1.88-2.32 (1H,m), 3.65 (2H,d,J=2.0Hz), 3.74 (2H,d,J=6.3Hz), 6.83-6.99 (2H,m), 7.12-7.28 (2H,m), 9.70 (1H,t,J=2.0Hz)

10 Referential Example 32

The procedure of Referential Example 31 is repeated to obtain 2-(2-isopentyloxyphenyl)ethanal.

NMR (CDCl₃) δ: 0.95 (6H,d,J=6.9Hz), 1.56-1.95 (3H,m), 3.63 (2H,d,J=2.2Hz), 4.02 (2H,t,J=6.6Hz), 6.83-7.01
 15 (2H,m), 7.10-7.34 (2H,m), 9.68 (1H,t,J=2.2Hz)

Referential Example 33

The procedure of Referential Example 11 is repeated to obtain ethyl 3-(2-isopentyloxyphenyl)-2-propenoate.

20 NMR (CDCl₃) δ: 0.98 (6H,d,J=6.1Hz), 1.33 (3H,t,J=6.9Hz), 1.70-1.98 (3H,m), 3.99-4.37 (4H,m), 6.52 (1H,d,J=16.4Hz), 6.93 (2H,t,J=6.4Hz), 7.23-7.54 (2H,m), 8.00 (1H,t,J=8.5Hz)

Referential Example 34

25 The procedure of Referential Example 11 is

repeated to obtain ethyl 4-(2-isobutoxyphenyl)-2-butenolate.

NMR (CDCl₃) δ: 1.03 (6H,d,J=6.8Hz), 1.26 (3H,t,J=7.1Hz),
1.89-2.32 (1H,m), 3.53 (2H,dd,J=5.9,1.0Hz), 3.73
5 (2H,d,J=6.1Hz), 4.16 (2H,q,J=7.1Hz), 5.78
(1H,dt,J=15.4,1.3Hz), 6.79-6.94 (2H,m), 7.09
(1H,dd,J=6.4,2.0Hz), 7.21-7.29 (2H,m)

Referential Example 35

The procedure of Referential Example 11 is
10 repeated to obtain ethyl 4-(2-isopentyloxyphenyl)-2-butenolate.

NMR (CDCl₃) δ: 0.95 (6H,d,J=6.9Hz), 1.26 (3H,t,J=7.1Hz),
1.60-1.90 (3H,m), 3.05 (2H,dd,J=6.6,1.2Hz), 3.98
(2H,t,J=5.6Hz), 4.17 (2H,q,J=7.1Hz), 5.78 (1H,dt,
15 J=15.6,1.5Hz), 6.78-6.94 (2H,m), 7.02-7.34 (3H,m)

Referential Example 36

The procedure of Referential Example 12 is
repeated to obtain ethyl 3-(2-isopentyloxyphenyl)-propanoate.

20 NMR (CDCl₃) δ: 0.97 (6H,d,J=5.9Hz), 1.23 (3H,t,J=7.1Hz),
1.60-2.03 (3H,m), 2.49-2.68 (2H,m), 2.85-3.05 (2H,m),
3.92-4.24 (4H,m), 6.76-6.91 (2H,m), 7.09-7.24 (2H,m)

Referential Example 37

The procedure of Referential Example 12 is
25 repeated to obtain ethyl 4-(2-isobutoxyphenyl)-

butanoate.

NMR (CDCl₃) δ : 1.05 (6H,d,J=6.6Hz), 1.24 (3H,t,J=7.1Hz),
 1.83-2.18 (3H,m), 2.33 (2H,t,J=6.6Hz), 2.68
 (2H,t,J=7.1Hz), 3.72 (2H,d,J=6.1Hz), 4.11
 5 (2H,q,J=7.1Hz), 6.84 (2H,t,J=5.9Hz), 7.08-7.23 (2H,m)

Referential Example 38

In 170 ml of ethanol is dissolved 16.7 g of
 3-(3-ethoxy-3-oxopropyl)-4-[4-nitrobenzyloxy]benzoic
 acid, to which is added 1.7 g of 5% palladium-carbon.
 10 The mixture thus obtained is stirred at ambient
 temperature for 5 hours in a stream of hydrogen. The
 reaction mixture is filtered with Celite and the
 solvent is distilled off from the filtrate to obtain
 7.5 g of 3-(3-ethoxy-3-oxopropyl)-4-hydroxybenzoic
 15 acid as a light brown solid product.
 NMR (CDCl₃) δ : 1.16 (3H,t,J=7.1Hz), 2.52-2.84 (4H,m),
 4.05 (2H,q,J=7.1Hz), 6.94 (1H,d,J=9.1Hz), 7.65-7.73
 (4H,m)

Referential Example 39

20 In 75 ml of N,N-dimethylformamide are
 suspended 7.5 g of 3-(3-ethoxy-3-oxopropyl)-4-
 hydroxybenzoic acid, 17.5 g of potassium carbonate and
 7.4 ml of acetic anhydride. The mixture thus obtained
 is stirred at ambient temperature for 2 hours. The
 25 reaction mixture is added to a mixture of ethyl acetate
 and water, pH is adjusted to 2 with 6 mol/L

hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 5:1) to obtain 1.8 g of 4-(acetyloxy)-3-(3-ethoxy-3-oxopropyl)benzoic acid as a light brown-colored solid product.

10 NMR (CDCl₃) δ : 1.25 (3H,t,J=7.1Hz), 2.37 (3H,s), 2.51-2.70 (2H,m), 2.86-3.01 (2H,m), 4.15 (2H,q,J=7.1Hz), 7.17 (1H,d,J=9.3Hz), 7.95-8.05 (3H,m)

Referential Example 40

In a mixture of 15 ml of ethyl acetate and 15 ml of ethanol is dissolved 5.00 g of methyl 4-(benzyloxy)-2-isobutoxybenzoate, to which is added 1.0 g of 5% palladium-carbon. The mixture thus obtained is stirred at ambient temperature for 3 hours in a stream of hydrogen. The reaction mixture is filtered with Celite, and the solvent is distilled off therefrom under reduced pressure. Then, 19 ml of 5 mol/L solution of sodium hydroxide is added to a solution of the residue obtained above in 35 ml of ethanol, and the mixture thus obtained is stirred at 50°C for one hour.

25 The reaction mixture is added to a mixture of chloroform and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated.

To a solution of the residue thus obtained in 20 ml of tetrahydrofuran are successively added 2.0 ml of triethylamine and 0.8 ml of acetyl chloride, and the mixture thus obtained is stirred at ambient temperature for 10 minutes. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 1.37 g of 4-acetyloxy-2-isobutoxybenzoic acid is obtained as a light yellow oily product.

15 NMR (CDCl₃) δ : 1.05 (6H,d,J=6.6Hz), 1.92-2.40 (1H,m), 2.31 (3H,s), 3.78 (2H,d,J=6.4Hz), 6.68-6.83 (3H,m), 7.89 (1H,d,J=9.0Hz)

Referential Example 41

In 50 ml of N,N-dimethylformamide are suspended 5.0 g of 3,5-dihydroxybenzoic acid, 29.8 g of potassium carbonate and 11 ml of isobutyl iodide. The mixture thus obtained is stirred at 110°C for 7 hours. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and

dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to
 5 obtain 2.6 g of isobutyl 3,5-diisobutoxybenzoate as a light yellow oily product.

NMR (CDCl₃) δ : 1.02 (18H,d,J=6.6Hz), 1.85-2.30 (3H,m), 3.74 (4H,d,J=6.6Hz), 4.09 (2H,d,J=6.6Hz), 6.62-6.67 (1H,m), 7.16 (2H,d,J=2.2Hz)

10 Referential Example 42

In 13 ml of methanol is dissolved 2.5 g of isobutyl 3,5-diisobutoxybenzoate, to which is then added 2.3 ml of 5 mol/L sodium hydroxide solution. The mixture thus obtained is stirred at 50°C for 3 hours.

15 Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous
 20 magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 1.8 g of 3,5-diisobutoxybenzoic acid is obtained as a white solid product.

NMR (CDCl₃) δ : 1.03 (12H,d,J=6.6Hz), 1.87-2.33 (2H,m),
 25 3.76 (4H,d,J=6.4Hz), 6.65-7.24 (4H,m)

Referential Example 43

In 200 ml of N,N-dimethylformamide are suspended 10 g of 2,5-dihydroxybenzoic acid, 148 g of potassium carbonate and 106 ml of isobutyl bromide.

- 5 The mixture is stirred at 110°C for 6 hours. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to
- 10 obtain 18 g of isobutyl 2,5-diisobutoxybenzoate as a light yellow oily product.

NMR (CDCl₃) δ: 0.97-1.06 (18H,m), 1.60-2.40 (3H,m), 3.69 (2H,d,J=6.3Hz), 3.73 (2H,d,J=6.6Hz), 4.09 (2H,d,J=6.6Hz), 6.80-7.05 (2H,m), 7.31 (1H,d,J=2.7Hz)

20 Referential Example 44

In 88 ml of ethanol is dissolved 17.48 g of isobutyl 2,5-diisobutoxybenzoate. After adding 33 ml of 5 mol/L sodium hydroxide solution, the mixture is stirred at ambient temperature for 30 minutes.

- 25 Chloroform and water are added to the reaction mixture, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is

washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 12.16 g of 2,5-
 5 diisobutoxybenzoic acid is obtained as a white solid product.

NMR (CDCl_3) δ : 1.01 (6H,d,J=6.4Hz), 1.08 (6H,d,J=6.4Hz),
 1.80-2.48 (2H,m), 3.73 (2H,d,J=6.5Hz), 3.98
 (2H,d,J=6.4Hz), 6.91-7.18 (2H,m), 7.66 (1H,d,J=3.0Hz),
 10 10.74 (1H,brs)

Referential Example 45

In 50 ml of N,N-dimethylformamide are suspended 5.0 g of 3,4-dihydroxybenzaldehyde, 15.5 g of potassium carbonate and 14 ml of isopentyl iodide. The
 15 mixture is stirred at 60°C for 2 hours. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer is washed with water and saturated aqueous
 20 solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 10:1) to
 25 obtain 9.4 g of 3,4-diisopentyloxybenzaldehyde as a light yellow oily product.

NMR (CDCl_3) δ : 0.98 (12H,d,J=6.1Hz), 1.63-1.81 (6H,m),

4.01-4.18 (4H,m), 6.95 (1H,d,J=8.8Hz), 7.36-7.46
(2H,m), 9.83 (1H,s)

Referential Example 46

The procedure of Referential Example 45 is
5 repeated to obtain isobutyl 3,4-diisobutoxybenzoate.
NMR (CDCl₃) δ: 0.88-1.09 (18H,m), 1.93-2.31 (3H,m), 3.80
(4H,d,J=6.3Hz), 4.08 (2H,d,J=6.6Hz), 6.85
(1H,d,J=8.3Hz), 7.54 (1H,d,J=2.0Hz), 7.64
(1H,dd,J=8.3,2.0Hz)

10 Referential Example 47

In 30 ml of acetonitrile is dissolved 3.0 g
of 3,4-diisopentyloxybenzaldehyde, to which are
successively added at ambient temperature a solution of
4.5 g of sodium dihydrogenphosphate in 15 ml of water
15 and 1.8 ml of 30% aqueous hydrogen peroxide. Then, a
solution of 2.0 g of sodium chlorite in 30 ml of water
is dropwise added thereto at 5-10°C, and the mixture
thus obtained is stirred at ambient temperature for 3.5
hours. Chloroform and water are added to the reaction
20 mixture, pH is adjusted to 2 with 6 mol/L hydrochloric
acid, and the organic layer is separated. The organic
layer thus obtained is washed with water and saturated
aqueous solution of sodium chloride successively and
dried over anhydrous magnesium sulfate, and then the
25 solvent is distilled off under reduced pressure. Thus,
3.0 g of 3,4-diisopentyloxybenzoic acid is obtained as

a white solid product.

NMR (CDCl₃) δ : 0.98 (12H,d,J=5.4Hz), 1.60-1.90 (6H,m),
4.02-4.09 (4H,m), 6.90 (1H,d,J=8.8Hz), 7.60-7.80 (3H,m)

Referential Example 48

- 5 In 50 ml of N,N-dimethylformamide are
suspended 5.0 g of 3,4-dihydroxybenzaldehyde, 10.0 g of
potassium carbonate and 8.3 ml of isobutyl iodide. The
suspension is stirred at 80°C for 2 hours. The reaction
mixture is added to a mixture of ethyl acetate and
10 water, pH is adjusted to 2 with 6 mol/L hydrochloric
acid, and the organic layer is separated. The organic
layer thus obtained is washed with water and saturated
aqueous solution of sodium chloride successively and
dried over anhydrous magnesium sulfate, and then the
15 solvent is distilled off under reduced pressure. The
residue thus obtained is purified by silica gel column
chromatography (eluent; hexane:ethyl acetate = 5:1) to
obtain 3.3 g of 3-hydroxy-4-isobutoxybenzaldehyde as a
light yellow solid product.
- 20 NMR (CDCl₃) δ : 1.06 (6H,d,J=6.6Hz), 1.96-2.41 (1H,m),
3.91 (2H,d,J=6.6Hz), 5.80 (1H,s), 6.94 (1H,d,J=8.8Hz),
7.36-7.46 (2H,m), 9.84 (1H,s)

Referential Example 49

- The Procedure of Referential Example 48 is
25 repeated to obtain 3-hydroxy-4-isopentyloxy-
benzaldehyde.

NMR (CDCl₃) δ : 0.99 (6H,d,J=5.9Hz), 1.62-1.91 (3H,m),
4.17 (2H,t,J=6.6Hz), 5.85 (1H,s), 6.96 (1H,d,J=8.8Hz),
7.36-7.45 (2H,m), 9.84 (1H,s)

Referential Example 50

5 In 31 ml of N,N-dimethylformamide are
suspended 3.1 g of 3-hydroxy-4-isobutoxybenzaldehyde,
0.7 g of 60% sodium hydride and 3 ml of acetic
anhydride. The suspension is stirred for 2 hours at
100°C. The reaction mixture is added to a mixture of
10 ethyl acetate and water, pH is adjusted to 2 with 6
mol/L hydrochloric acid, and the organic layer is
separated. The organic layer thus obtained is washed
with water and saturated aqueous solution of sodium
chloride successively and dried over anhydrous
15 magnesium sulfate, and then the solvent is distilled
off under reduced pressure. Thus, 4.2 g of 5-formyl-2-
isobutoxyphenyl acetate is obtained as a yellow oily
product.

NMR (CDCl₃) δ : 1.02 (6H,d,J=6.6Hz), 1.98-2.40 (1H,m),
20 2.32 (3H,s), 3.84 (2H,d,J=6.4Hz), 7.04 (1H,d,J=8.3Hz),
7.58 (1H,d,J=2.0Hz), 7.74 (1H,dd,J=8.3,2.0Hz), 9.86
(1H,s)

Referential Example 51

The procedure of Referential Example 50 is
25 repeated to obtain ethyl 2-(5-formyl-2-
isobutoxyphenoxy)acetate.

NMR (CDCl₃) δ : 0.96 (6H,d,J=6.1Hz), 1.27 (3H,t,J=7.1Hz),
 1.70-1.83 (3H,m), 4.11 (2H,t,J=6.8Hz), 4.24
 (2H,q,J=7.1Hz), 4.69 (2H,s), 6.97 (1H,d,J=8.3Hz), 7.33
 (1H,d,J=1.7Hz), 7.47 (1H,dd,J=8.2,1.7Hz), 9.79 (1H,s)

5 Referential Example 52

In 38 ml of acetonitrile is dissolved 4.1 g
 of 5-formyl-2-isobutoxyphenyl acetate. To the solution
 thus obtained, 6.8 g of sodium dihydrogenphosphate
 dissolved in 20 ml of water and 3.6 ml of 30% aqueous
 10 hydrogen peroxide are successively added at ambient
 temperature, and then 3.6 g of sodium chlorite
 dissolved in 18 ml of water is dropwise added at 5-10°C.
 The mixture thus obtained is stirred at ambient
 temperature for 2 hours. Chloroform and water are
 15 added to the reaction mixture, the organic layer is
 separated, the organic layer thus obtained is washed
 successively with 5% aqueous solution of sodium
 thiosulfate and saturated aqueous solution of sodium
 chloride, dried over anhydrous magnesium sulfate, and
 20 then the solvent is distilled off under reduced
 pressure. Thus, 4.0 g of 3-(acetyloxy)-4-
 isobutoxybenzoic acid is obtained as a light yellow
 solid product.

NMR (CDCl₃) δ : 1.02 (6H,d,J=6.6Hz), 1.90-2.30 (1H,m),
 25 2.32 (3H,s), 3.82 (2H,d,J=6.3Hz), 6.97 (1H,d,J=8.5Hz),
 7.79 (1H,d,J=2.2Hz), 7.99 (1H,dd,J=8.7,2.2Hz), 11.85
 (1H,brs)

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Referential Example 53

The procedure of Referential Example 52 is repeated to obtain 3-(2-ethoxy-2-oxoethoxy)-4-isopentyloxybenzoic acid.

5 NMR (CDCl₃) δ: 0.98 (6H,d,J=5.9Hz), 1.31 (3H,t,J=7.3Hz), 1.64-1.85 (3H,m), 4.13 (2H,t,J=6.8Hz), 4.28 (2H,q,J=7.3Hz), 4.71 (2H,s), 6.94 (1H,d,J=8.6Hz), 7.58 (1H,d,J=2.0Hz), 7.80 (1H,dd,J=8.4,2.0Hz), 8.53 (1H,brs)

Referential Example 54

10 In 30 ml of N,N-dimethylformamide are suspended 2.81 g of ethyl 5-methyl-1H-indole-2-carboxylate, 17.0 g of potassium carbonate and 11.3 ml of isobutyl iodide. The suspension is stirred at 120°C for one hour. The reaction mixture is added to a
15 mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled
20 off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent: toluene) to obtain 1.75 g of ethyl 1-isobutyl-5-methyl-1H-indole-2-carboxylate as a light yellow oily product.

25 NMR (CDCl₃) δ: 0.87 (6H,d,J=6.6Hz), 1.39 (3H,t,J=7.1Hz), 1.90-2.50 (1H,m), 2.43 (3H,s), 4.35 (2H,q,J=7.1Hz), 4.36 (2H,d,J=7.6Hz), 7.06-7.42 (4H,m)

Referential Example 55

In 10 ml of benzene are suspended 1.00 g of ethyl 1-isobutyl-5-methyl-1H-indole-2-carboxylate, 0.76 g of N-bromosuccinimide and 0.07 g of 2,2'-

5 azobisisobutyronitrile. The suspension is heated under reflux for two hours. The reaction mixture is concentrated under reduced pressure, and the residue thus obtained is dissolved in 10 ml of N,N-dimethylformamide. After adding 0.57 g of potassium

10 acetate, the mixture is stirred at 40°C for 30 minutes. The reaction mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride

15 successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 6:1) to obtain 0.68 g of ethyl

20 3-bromo-5-formyl-1-isobutyl-1H-indole-2-carboxylate as a yellow oily product.

NMR (CDCl₃) δ: 0.88 (6H,d,J=6.6Hz), 1.48 (3H,t,J=7.1Hz), 1.89-2.44 (1H,m), 4.37-4.51 (4H,m), 7.47 (1H,d,J=8.8Hz), 7.92 (1H,dd,J=8.9,1.5Hz), 8.20

25 (1H,d,J=0.7Hz), 10.08 (1H,s)

Referential Example 56

In 7 ml of acetonitrile is dissolved 0.65 g

of ethyl 3-bromo-5-formyl-1-isobutyl-1H-indole-2-carboxylate. To the solution are successively added at ambient temperature 1.56 g of sodium dihydrogen-phosphate dihydrate dissolved in 22 ml of water and

5 0.64 ml of 30% aqueous hydrogen peroxide. Then, 0.68 g of sodium chlorite dissolved in 20 ml of water is dropwise added thereto at 5-10°C. The mixture thus obtained is stirred at 60°C for one hour. Ethyl acetate and water are added to the reaction mixture, and the

10 organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.37 g of

15 3-bromo-2-(ethoxycarbonyl)-1-isobutyl-1H-indole-5-carboxylic acid is obtained as a yellow solid product. NMR (CDCl₃) δ: 0.88 (6H,d,J=6.6Hz), 1.48 (3H,t,J=7.1Hz), 1.87-2.33 (1H,m), 4.35-4.58 (4H,m), 5.62 (1H,brs), 7.43 (1H,d,J=9.0Hz), 8.10 (1H,dd,J=8.8, 1.5Hz), 8.54

20 (1H,d,J=1.0Hz)

Referential Example 57

In 6 ml of N,N-dimethylformamide are suspended 0.30 g of 3-bromo-2-(ethoxycarbonyl)-1-isobutyl-1H-indole-5-carboxylic acid, 0.10 g of

25 tetrakis(triphenylphosphine)palladium(0), 0.24 ml of formic acid and 1.36 ml of triethylamine. The suspension is stirred at 80°C for 5 hours. The reaction

10 5 mixture is added to a mixture of ethyl acetate and water, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. The residue thus obtained is purified by silica gel column chromatography (eluent; hexane:ethyl acetate = 3:1) to obtain 0.12 g of 2-(ethoxycarbonyl)-1-isobutyl-1H-indole-5-carboxylic acid as a yellow solid product.

NMR (CDCl₃) δ: 0.90 (6H,d,J=6.6Hz), 1.43 (3H,t,J=7.1Hz), 2.00-2.47 (1H,m), 4.27-4.51 (4H,m), 7.39-7.48 (3H,m), 8.06 (1H,dd,J=8.9,1.5Hz), 8.54 (1H,d,J=1.2Hz)

Referential Example 58

15 In 10 ml of dioxane is added 1.00 g of 2-amino-3,5-dibromo-4-(methoxycarbonyl)benzoic acid, to which are successively added 0.6 ml of triethylamine and 0.9 ml of diphenyl phosphoryl azide. The mixture thus obtained is heated under reflux for 1.5 hours.

20 Ethyl acetate and water are added to the reaction mixture, pH is adjusted to 6 with 6 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.96 g of methyl 4,6-dibromo-2-oxo-2,3-dihydro-1H-

benzimidazole-5-carboxylate is obtained as a light brown-colored solid product.

NMR (DMSO-d₆) δ : 3.94 (3H,s), 7.13-7.18 (1H,m), 11.00 (2H,brs)

5 Referential Example 59

10 In 10 ml of N,N-dimethylformamide are suspended 0.95 g of methyl 4,6-dibromo-2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate, 0.24 g of 60% sodium hydride and 0.7 ml of isopentyl bromide. The suspension is stirred at 50-60°C for 3 hours. The reaction mixture is added to a mixture of ethyl acetate and water, pH is adjusted to 2 with 2 mol/L hydrochloric acid, and the organic layer is separated. The organic layer thus obtained is washed with water and saturated aqueous solution of sodium chloride

15 successively and dried over anhydrous magnesium sulfate, and then the solvent is distilled off under reduced pressure. Thus, 0.71 g of methyl 4,6-dibromo-1,3-diisopentyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-

20 carboxylate is obtained as a light brown-colored solid product.

NMR (CDCl₃) δ : 0.98 (12H,d,J=5.6Hz), 1.43-1.77 (6H,m), 3.77-3.93 (2H,m), 3.98 (3H,s), 4.15-4.32 (2H,m), 7.08 (1H,s)

25 Referential Example 60

 In 7 ml of N,N-dimethylformamide are

suspended 0.70 g of methyl 4,6-dibromo-1,3-diisopentyl-
2-oxo-2,3-dihydro-1H-benzimidazole-5-carboxylate, 0.16
g of tetrakis(triphenylphosphine)palladium(0), 0.44 ml
of formic acid and 2.4 ml of triethylamine. The
5 suspension is stirred at 100°C for 3 hours. The
reaction mixture is added to a mixture of ethyl acetate
and water, pH is adjusted to 4 with 2 mol/L
hydrochloric acid, and the organic layer is separated.
The organic layer thus obtained is washed with water
10 and saturated aqueous solution of sodium chloride
successively and dried over anhydrous magnesium
sulfate, and then the solvent is distilled off under
reduced pressure. The residue thus obtained is
purified by silica gel column chromatography (eluent;
15 hexane:ethyl acetate = 5:1) to obtain 0.37 g of methyl
1,3-diisopentyl-2-oxo-2,3-dihydro-1H-benzimidazole-5-
carboxylate as a colorless oily product.
NMR (CDCl₃) δ: 0.98 (12H,d,J=5.4Hz), 1.48-1.88 (6H,m),
3.84-3.93 (4H,m), 3.93 (3H,s), 6.98 (1H,d,J=8.3Hz),
20 7.67 (1H,s), 7.84 (1H,dd,J=8.2,1.2Hz)

Referential Example 61

In 7 ml of methanol is dissolved 0.34 g of
methyl 1,3-diisopentyl-2-oxo-2,3-dihydro-1H-
benzimidazole-5-carboxylate. After adding 1.5 ml of 1
25 mol/L solution of sodium hydroxide, the mixture is
stirred at 50°C for one hour. Water and chloroform are
successively added to the reaction mixture, pH is

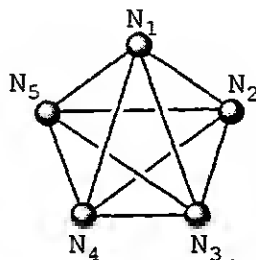
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This invention relates to a compound having an inhibitory action on the activity of transcription factor AP-1 or a salt thereof, an agent for preventing and treating diseases into which an excessive expression of AP-1 participates which contains said compound or said salt, and an AP-1 inhibiting agent. The compounds and agents of this invention are useful as therapeutic and preventive drugs causing lessened side reactions.

15
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CLAIMS

1. A compound comprising the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 , said atoms constitute the pharmacophore represented by the following formula 1:



wherein N_1 represents an atom to which a donative hydrogen atom in a hydrogen-bond donating group is bonded or a hydrogen-bond accepting atom in a hydrogen-bond accepting group; N_3 represents a hydrogen-bond accepting atom in a hydrogen-bond accepting group; and N_2 , N_4 and N_5 independently represent an arbitrary carbon atom constituting a hydrophobic group and the distance between N_1 and N_2 is not less than 5 angstroms and not more than 12 angstroms, the distance between N_1 and N_3 is not less than 9 angstroms and not more than 15 angstroms, the distance between N_1 and N_4 is not less than 3 angstroms and not more than 13 angstroms, the distance between N_1 and N_5 is not less than 8 angstroms and not more than 16 angstroms, the distance between N_2 and N_3 is not less than 3 angstroms and not more than 10 angstroms, the distance between N_2 and N_4 is not less than 6 angstroms and not more than 14 angstroms, the

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distance between N_2 and N_5 is not less than 9 angstroms and not more than 14 angstroms, the distance between N_3 and N_4 is not less than 4 angstroms and not more than 11 angstroms, the distance between N_3 and N_5 is not less than 3 angstroms and not more than 10 angstroms, and the distance between N_4 and N_5 is not less than 4 angstroms and not more than 9 angstroms; and, in the optimized three-dimensional structure thereof, the distances between the atom corresponding to N_3 and the two or more atoms selected from N_1 , N_2 , N_4 and N_5 are the interatomic distances in the pharmacophore; and a salt thereof.

2. A compound or a salt thereof according to Claim 1, wherein, for each of the atoms constituting the pharmacophore, the distance between N_1 and N_2 is not less than 5.09 angstroms and not more than 11.67 angstroms, the distance between N_1 and N_3 is not less than 9.47 angstroms and not more than 14.30 angstroms, the distance between N_1 and N_4 is not less than 3.48 angstroms and not more than 12.60 angstroms, the distance between N_1 and N_5 is not less than 8.77 angstroms and not more than 15.67 angstroms, the distance between N_2 and N_3 is not less than 3.78 angstroms and not more than 9.78 angstroms, the distance between N_2 and N_4 is not less than 6.97 angstroms and not more than 13.26 angstroms, the distance between N_2 and N_5 is not less than 9.37 angstroms and not more than 13.32 angstroms, the

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distance between N_3 and N_4 is not less than 4.83 angstroms and not more than 10.51 angstroms, the distance between N_3 and N_5 is not less than 3.31 angstroms and not more than 9.97 angstroms, and the distance between N_4 and N_5 is not less than 4.32 angstroms and not more than 8.25 angstroms.

3. A compound or a salt thereof according to Claim 1 or 2, wherein N_1 constituting the pharmacophore is a nitrogen atom of unsubstituted or substituted amino, ammonium, amido, thioamido, ureido, isoureido, amidino, guanidino, thioureido, hydrazino or hydrazono group to which one or more hydrogen atoms are bonded, a carbon atom of ethenyl group to which a hydrogen atom is bonded, an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfonyl group, an oxygen atom of sulfonyloxy group, an oxygen atom of sulfo group, an oxygen atom of sulfinyl group, an oxygen atom of carboxyl group, an oxygen atom of ether, a sulfur atom of thioether, a sulfur atom of mercapto group, an oxygen atom of hydroxyl group, an oxygen atom of ester or a nitrogen atom of unsubstituted or substituted nitrogen-containing heterocyclic group; N_3 is an oxygen atom of carbonyl group, a sulfur atom of thiocarbonyl group, a nitrogen atom of unsubstituted or substituted imino group, an oxygen atom of sulfo group, an oxygen atom of sulfonyl group, an oxygen atom of sulfo group, an

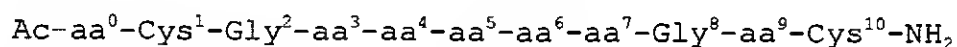
4. A compound or a salt thereof according to any one of Claims 1 to 3, wherein a compound having an atom corresponding to N₃ and atoms corresponding to two or more atoms selected from N₁, N₂, N₄ and N₅ among the atoms N₁, N₂, N₃, N₄ and N₅ constituting a pharmacophore, and, in the optimized three-dimensional structure thereof, the interatomic distances between the atom corresponding to N₃ and the two or more atoms selected from N₁, N₂, N₄ and N₅ are the atomic distances of a pharmacophore has an activity of antagonistically inhibiting the binding between AP-1 (activator protein-1) and a recognition sequence thereof.

Ac-Cys¹-Gly²-AA³-AA⁴-AA⁵-AA⁶-AA⁷-AA⁸-Gly⁹-Cys¹⁰-NH₂
wherein Ac represents an acetyl group, AA³ represents a polar amino acid residue, each of AA⁴, AA⁶ and AA⁷

represents a hydrophobic amino acid residue, AA⁵ represents an amino acid residue having carboxyl or hydroxyl group in the side chain thereof, and AA⁸ represents an arbitrary amino acid residue; said peptide having a disulfide linkage between the first and tenth cysteine residues; or a salt thereof.

6. A peptide or a salt thereof according to Claim 5, wherein AA³ is an L-asparagine residue or an L-glutamine residue; AA⁴, AA⁶ and AA⁷ are an L-leucine residue, an L-isoleucine residue, an L-alanine residue or an L-valine residue; and AA⁵ is an L-aspartic acid residue, an L-glutamic acid residue, an L-serine residue or an L-threonine residue.

7. A peptide of 10 or 11 residues represented by the following amino acid sequence:



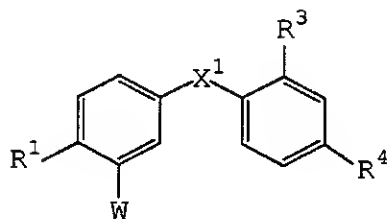
wherein Ac represents an acetyl group, aa⁰ represents an arbitrary amino acid residue or a bonding unit, aa³ represents a polar amino acid residue, each of aa⁴, aa⁵ and aa⁷ represents a hydrophobic amino acid residue, aa⁶ represents an arbitrary amino acid residue, and aa⁹ represents an amino acid residue having carboxyl or hydroxyl group in the side chain thereof; provided that, when aa⁰ is a bonding unit, said peptide has a disulfide linkage between the first and tenth cysteine residues and, when aa⁰ is an arbitrary amino acid residue, said peptide has a disulfide linkage between the second and eleventh cysteine residues; or a salt

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thereof.

8. A peptide or a salt thereof according to Claim 7, wherein aa³ is an L-asparagine acid residue or an L-glutamine acid residue; aa⁴, aa⁵ and aa⁷ are an L-leucine residue, an L-isoleucine residue, an L-alanine residue or an L-valine residue; and aa⁹ is an L-aspartic acid residue, an L-glutamic acid residue, an L-serine residue or an L-threonine residue.

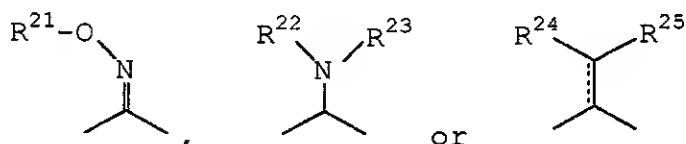
9. A benzene derivative represented by the following general formula:



wherein R¹ represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R³ represents a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or

protected amino group, a mercapto group, a carbamoyl group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^4 represents a hydrogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group;

X^1 represents $-C(O)-$, $-CH(OH)-$, $-CH_2-$ or a group of the following formula:



wherein R^{21} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group; R^{22} and R^{23} may be the same or different represent a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, carbamoyl,

alkylsulfinyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; and R^{24} and R^{25} may be the same or different represent a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; the double line of which one line is a broken line denotes a single bond or a double bond; and

W represents $-Z-COR^{26}$, $-Z-COOR^2$, $-O-CH_2COOR^2$ or $-O-CH_2CH_2COOR^2$ [wherein Z represents $-(CH_2)_n-$ in which n represents 0, 1, 2 or 3, $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; R^2 represents a hydrogen atom or a protecting group for carboxyl group; and R^{26} represents $-NHR^{27}$ or $-NHSO_2R^{28}$ in which R^{27} and R^{28} independently represent an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group];

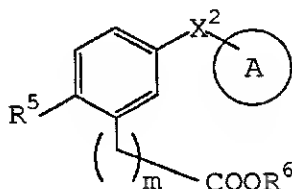
or a salt thereof.

10. A benzene derivative or a salt thereof according to Claim 9, wherein W is $-Z'-COOR^{2'}$, $-Z'-CONH-SO_2R^{28'}$, $-CONH-CH_2COOR^{2'}$ or $-CONH-CH_2CH_2COOR^{2'}$ [wherein Z' represents $-(CH_2)_{n'}-$ in which n' is 0, 1 or 2, or $-CH=CH-$; $R^{28'}$ represents an unsubstituted or substituted alkyl

group; and $R^{2'}$ represents a hydrogen atom or a protecting group for carboxyl group]; and X^1 is $-C(O)-$, $-CH(OH)-$ or $-CH_2-$.

11. A benzene derivative or a salt thereof according to Claim 10, wherein R^1 is an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group; R^3 is an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group; and R^4 is an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group.

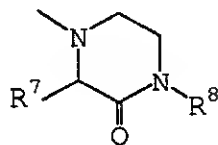
12. A benzene derivative represented by the following general formula:



wherein R^5 represents a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^6 represents a

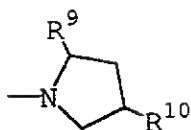
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hydrogen atom or a protecting group for carboxyl group;
 X^2 represents $-C(O)-$; m represents 0, 1 or 2; and ring A
 represents a group represented by the following
 formula:



wherein R^7 represents a hydrogen atom, a halogen atom, a
 cyano group, a nitro group, an unprotected or protected
 carboxyl group, an unprotected or protected hydroxyl
 group, an unprotected or protected amino group, a
 mercapto group or an unsubstituted or substituted
 alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy,
 aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl,
 carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl,
 alkylamino, acylamino, alkylsulfonylamino,
 arylsulfonylamino or heterocyclic group; and R^8
 represents a hydrogen atom, an unprotected or protected
 amino group or an unsubstituted or substituted alkyl,
 alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy,
 acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl,
 alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino,
 acylamino, alkylsulfonylamino, arylsulfonylamino or
 heterocyclic group; or a group of the following
 formula:

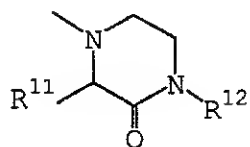
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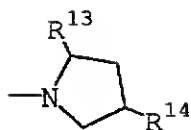
wherein R^9 and R^{10} may be the same or different represent a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino, alkanoyloxy or heterocyclic group;

or a salt thereof.

13. A benzene derivative or a salt thereof according to Claim 12, wherein R^5 is an alkoxy group or an acylamino group; X^2 is $-C(O)-$; and ring A is a group of the following formula:

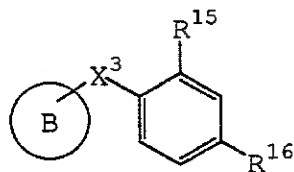


wherein R^{11} is an alkyl or alkoxycarbonyl group; and R^{12} is an alkyl group; or a group of the following formula:

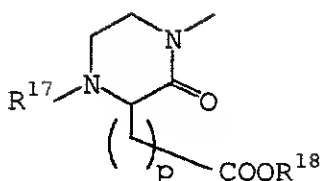


wherein R^{13} is an alkyl or alkoxy carbonyl group; and R^{14} is an alkoxy or alkanoyloxy group.

14. A benzene derivative represented by the following general formula:



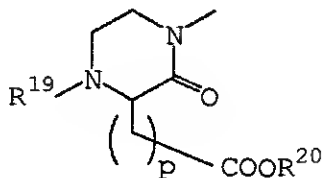
wherein R^{15} and R^{16} may be the same or different represent a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxy carbonyl, aryloxy carbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^3 represents $-C(O)-$; and ring B represents a group of the following formula:



wherein R^{17} represents a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylsulfonyl or heterocyclic group; R^{18} represents a hydrogen atom or a protecting group for carboxyl group; and p represents 0, 1 or 2;

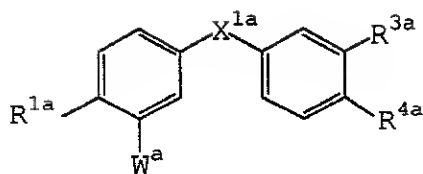
or a salt thereof.

15. A benzene derivative or a salt thereof according to Claim 14, wherein R^{15} and R^{16} may be the same or different represent an alkoxy group; and ring B represents a group of the following formula:

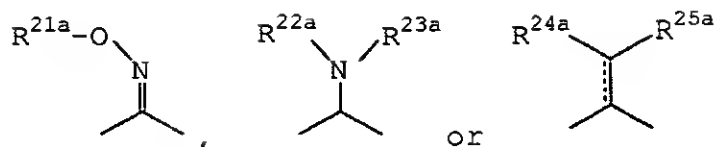


wherein R^{19} is an acyl group; R^{20} is a protecting group for carboxyl group; and p is 0, 1 or 2.

16. A benzene derivative represented by the following formula:



wherein R^{1a} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{3a} and R^{4a} may be the same or different represent a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1a} represents -C(O)-, -CH(OH)-, -CH₂- or a group of the following formula:

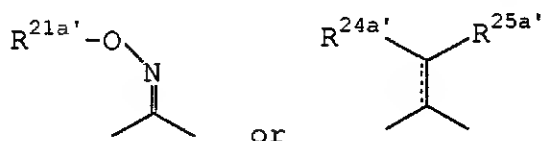


wherein R^{21a} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl or heterocycle-lower alkyl group; R^{22a} and R^{23a} may be the same or different represent a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, carbamoyl, alkylsulfinyl, alkylsulfonyl, arylsulfonyl or heterocyclic group; R^{24a} and R^{25a} may be the same or different represent a hydrogen atom, a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; and the double line of which one line is a broken line represents a single bond or a double bond; and W^a represents $-Z^a-$ COR^{26a} , $-Z^a-COOR^{2a}$, $-O-CH_2COOR^{2a}$ or $-O-CH_2CH_2COOR^{2a}$ [wherein Z^a represents $-(CH_2)_n^a$ (n^a is 0, 1, 2 or 3), $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; R^{2a} represents a hydrogen atom or a protecting group for carboxyl group; and R^{26a} represents $-NHR^{27a}$ or $-NHSO_2R^{28a}$ in which R^{27a} and R^{28a}

independently represent an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group];

or a salt thereof.

17. A benzene derivative or a salt thereof according to Claim 16, wherein R^{1a} is an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group; R^{3a} and R^{4a} may be the same or different and represent an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group; X^{1a} is $-C(O)-$, $-CH(OH)-$, $-CH_2-$ or a group of the following formula:

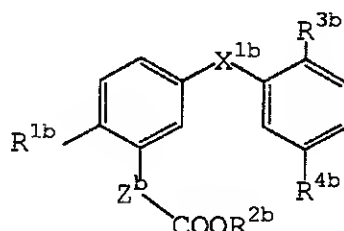


wherein $R^{21a'}$ represents an unsubstituted or substituted alkyl, aralkyl or heterocycle-lower alkyl group; $R^{24a'}$ and $R^{25a'}$ may be the same or different represent a hydrogen atom, an unprotected or protected carboxyl group or an unsubstituted or substituted alkyl, alkoxycarbonyl, aryloxycarbonyl or carbamoyl group; and W^a represents $-Z^a-COR^{26a'}$, $-Z^a-COOR^{2a'}$, $-O-CH_2COOR^{2a'}$, $-O-CH_2CH_2COOR^{2a'}$, $-CONH-CH_2COOR^{2a'}$, or $-CONH-CH_2CH_2COOR^{2a'}$ [wherein Z^a represents $-(CH_2)_n^a-$ in which n^a is 0, 1, 2' or 3, $-CH_2CH(CH_3)-$, $-CH=CH-$ or $-CH_2CH=CH-$; $R^{2a'}$ represents a hydrogen atom or a protecting group for carboxyl group; and $R^{26a'}$ represents $-NHSO_2R^{28a'}$ in which $R^{28a'}$ is an

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unsubstituted or substituted alkyl group].

18. A benzene derivative represented by the following general formula:



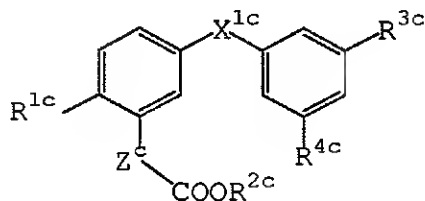
wherein R^{1b} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{2b} represents a hydrogen atom or a protecting group for carboxyl group; R^{3b} and R^{4b} may be the same or different represent a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino,

arylsulfonylamino or heterocyclic group; X^{1b} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^b represents $-(CH_2)_n-$ (n^b represents 0, 1 or 2) or $-CH=CH-$;

or a salt thereof.

19. A benzene derivative or a salt thereof according to Claim 18, wherein R^{1b} is an unsubstituted or substituted alkoxy group; R^{3b} and R^{4b} may be the same or different represent an unprotected or protected hydroxyl group or an unsubstituted or substituted alkoxy group; X^{1b} is $-C(O)-$; and Z^b is $-(CH_2)_2-$.

20. A benzene derivative represented by the following general formula:



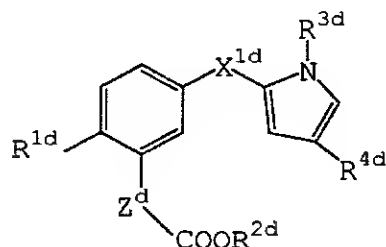
wherein R^{1c} represents a halogen atom, a cyano group, a nitro group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxy carbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{2c} represents a hydrogen atom or a protecting group for carboxyl group; R^{3c} and R^{4c} may be the same or different represent

a halogen atom, a cyano group, a nitro group, an unprotected or protected carboxyl group, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, acyl, alkoxycarbonyl, aryloxycarbonyl, carbamoyl, alkylthio, alkylsulfinyl, alkylsulfonyl, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1c} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^c represents $-(CH_2)_{n^c}-$ (n^c represents 0, 1 or 2) or $-CH=CH-$;

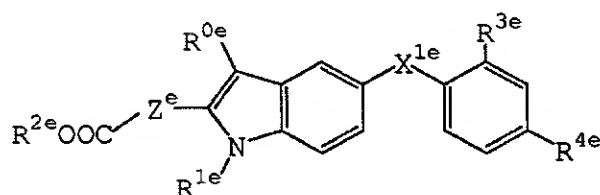
or a salt thereof.

21. A benzene derivative or a salt thereof according to Claim 20, wherein R^{1c} is an unsubstituted or substituted alkoxy group; R^{2c} is a hydrogen atom or a protecting group for carboxyl group; R^{3c} and R^{4c} may be the same or different represent an unsubstituted or substituted alkoxy group; X^{1c} represents $-C(O)-$; and Z^c represents $-(CH_2)_2-$.

22. A benzene derivative represented by the following general formula:



23. A benzene derivative or a salt thereof according to Claim 22, wherein R^{1d} is an unsubstituted or substituted alkoxy group; R^{3d} is an unsubstituted or substituted alkyl group; R^{4d} is an unsubstituted or substituted acyl group; X^{1d} is -C(O)-; and Z^d is -(CH₂)₂-.



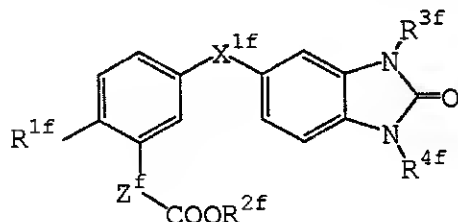
wherein R^{0e} represents a hydrogen atom, a halogen atom, a nitro group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl, alkylsulfonylamino or arylsulfonylamino group; R^{1e} represents an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, acyl, alkoxycarbonyl, aryloxycarbonyl or alkylsulfonyl group; R^{2e} represents a hydrogen atom or a protecting group for carboxyl group; R^{3e} and R^{4e} may be the same or different represent a hydrogen atom, a halogen atom, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; X^{1e} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^e represents $-(CH_2)_n-$ (n^e represents 0, 1 or 2) or $-CH=CH-$;

or a salt thereof.

25. A benzene derivative or a salt thereof according to Claim 24, wherein R^{0e} is a hydrogen atom or a halogen atom; R^{1e} is an unsubstituted or substituted

alkyl group; R^{3e} and R^{4e} independently represent an unsubstituted or substituted alkoxy group; X^{1e} is $-C(O)-$; and Z^e is a bonding unit.

26. A benzene derivative represented by the following general formula:



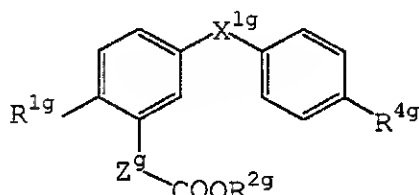
wherein R^{1f} represents a halogen atom, an unprotected or protected hydroxyl group, an unprotected or protected amino group, a mercapto group or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxy, aryloxy, alkylthio, alkylamino, acylamino, alkylsulfonylamino, arylsulfonylamino or heterocyclic group; R^{2f} represents a hydrogen atom or a protecting group for carboxyl group; R^{3f} and R^{4f} may be the same or different represent a hydrogen atom or an unsubstituted or substituted alkyl, alkenyl, cycloalkyl, aryl or aralkyl group; X^{1f} represents $-C(O)-$, $-CH(OH)-$ or $-CH_2-$; and Z^f represents $-(CH_2)_{n^f}-$ (n^f represents 1 or 2) or $-CH=CH-$;

or a salt thereof.

27. A benzene derivative or a salt thereof according to Claim 26, wherein R^{1f} is an unsubstituted or substituted alkoxy group; R^{3f} and R^{4f} independently

represent an unsubstituted or substituted alkyl group;
 X^{1f} is $-C(O)-$; and Z^f is $-CH_2-$.

28. A benzene derivative represented by the following general formula:



wherein R^{1g} and R^{4g} may be the same or different
 represent an unprotected or protected hydroxyl group or
 an unsubstituted or substituted alkoxy group; X^{1g} is -
 $C(O)-$, $-CH(OH)-$ or $-CH_2-$; Z^g is $-(CH_2)_n-$ (n^g represents
 1 or 2); and R^{2g} is a hydrogen atom or a protecting
 group for carboxyl group;

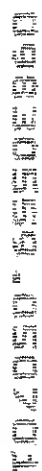
or a salt thereof.

29. A compound or a salt thereof according to any
 one of Claims 5 to 28, wherein said compound according
 to any one of Claims 5 to 28 is a compound that has an
 activity of antagonistically inhibiting the combination
 between AP-1 and a recognition sequence thereof.

30. A compound or a salt thereof according to
 Claim 1, wherein the compound conforming to a
 pharmacophore of Claim 1 is a peptide or a benzene
 derivative according to any one of Claims 5 to 28.

31. A method for inhibiting AP-1 which comprises
 administering a compound or a salt thereof according to
 any one of Claims 1 to 30.

32. An agent for preventing and treating a disease into which an excessive expression of AP-1 participates, which comprises a compound or a salt thereof according to any one of Claims 1 to 30.
33. An agent for preventing and treating an autoimmune disease, which comprises a compound or a salt thereof according to any one of Claims 1 to 30.
34. An AP-1 inhibitor comprising a compound or a salt thereof according to any one of Claims 1 to 30.

[illegible][illegible][illegible][illegible]



E5916-01 (*)

WE (I) the undersigned inventor(s), hereby declare(s) that:

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

the specification of which

- ☐ is attached hereto.
- ☐ was filed on _____ as
Application Serial No. _____
and amended on _____.
- ☒ was filed as PCT international application
Number _____ PCT/JP99/06166
on _____ November 5, 1999
and was amended under PCT Article ~~XX~~ 34
on _____ September 18, 2000 (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed	
10-328792	Japan	5 Nov., 1998	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
11-080693	Japan	25 March, 1999	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No
			<input type="checkbox"/> Yes	<input type="checkbox"/> No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisiona application(s) listed below.

(Application Number)

(Filing Date)

(Application Number)

(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.

Filing Date

Status (pending, patented, abandoned)

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; Vincent J. Sunderdick, Reg. No. 29,004; William E. Beaumont, Reg. No. 30,996; Robert F. Gnuse, Reg. No. 27,295; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Robert W. Hahl, Reg. No. 33,893; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,011; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Christina M. Gadiano, Reg. No. 37,628; Jeffrey B. McIntyre, Reg. No. 36,867; Paul E. Rauch, Reg. No. 38,591; William T. Enos, Reg. No. 33,128; and Michael E. McCabe, Jr., Reg. No. 37,182; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Hisaaki CHAKI
NAME OF FIRST SOLE INVENTOR

Residence: Kaminiikawa-gun,
Toyama, Japan

Hisaaki Chaki
Signature of Inventor

Citizen of: Japan

April 18, 2001
Date

Post Office Address: 455-1, Oharaya,
Ohyama-machi, Kaminiikawa-gun,
Toyama, Japan.

200 Tadakazu TAKAKURA
NAME OF SECOND JOINT INVENTOR

Tadakazu Takakura
Signature of Inventor

April 18, 2001
Date

300 Keiichi TSUCHIDA
NAME OF THIRD JOINT INVENTOR

Keiichi Tsuchida
Signature of Inventor

April 18, 2001
Date

400 Junichi YOKOTANI
NAME OF FOURTH JOINT INVENTOR

Junichi Yokotani
Signature of Inventor

April 18, 2001
Date

500 Hironori KOTSUBO
NAME OF FIFTH JOINT INVENTOR

Hironori Kotsubo
Signature of Inventor

April 18, 2001
Date

Residence: Toyama-shi, Toyama,
Japan JPX

Citizen of: Japan

Post Office Address: 26-2, Ohmachi,
Toyama-shi, Toyama, Japan.

Residence: Nei-gun, Toyama, Japan
JPX

Citizen of: Japan

Post Office Address: 427-23, Nishihongo,
Fuchu-machi, Nei-gun, Toyama,
Japan.

Residence: Toyama-shi, Toyama,
Japan JPX

Citizen of: Japan

Post Office Address: 1-6-27,
Shimookui, Toyama-shi, Toyama,
Japan.

Residence: Nakaniikawa-gun,
Toyama, Japan JPX

Citizen of: Japan

Post Office Address: 44-7,
Nishiashihara, Tateyama-machi,
Nakaniikawa-gun, Toyama, Japan.

600
Yukihiko AIKAWA
NAME OF SIXTH JOINT INVENTOR

Yukihiko Aikawa
Signature of Inventor

April 18, 2001
Date

700
Shuichi HIRONO
NAME OF SEVENTH JOINT INVENTOR

Shuichi Hirono
Signature of Inventor

April 18, 2001
Date

Shunichi SHIOZAWA
NAME OF EIGHTH JOINT INVENTOR

Shunichi Shiozawa
Signature of Inventor

April 18, 2001
Date

NAME OF NINTH JOINT INVENTOR

Signature of Inventor

Date

E5916-01
Residence: Toyama-shi, Toyama,
Japan JPX

Citizen of: Japan

Post Office Address: 230,
Mizuhashinakamura-machi,
Toyama-shi, Toyama, Japan.

Residence: Tokyo, Japan

Citizen of: Japan

Post Office Address: 16-29, 3-chome,
Akatsukashinmachi, Itabashi-ku,
Tokyo, Japan.

Residence: Kobe-shi, Hyogo, Japan

Citizen of: Japan

Post Office Address: 11-6, Takenodai
2-chome, Nishi-ku, Kobe-shi,
Hyogo, Japan.

Residence:

Citizen of:

Post Office Address: